

1 FOOD AND DRUG ADMINISTRATION  
2 CENTER FOR DRUG EVALUATION AND RESEARCH  
3  
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5 JOINT MEETING OF THE  
6 DRUG SAFETY AND RISK MANAGEMENT (DSaRM) and the  
7 ANESTHETIC AND ANALGESIC DRUG PRODUCTS (AADPAC)  
8 ADVISORY COMMITTEES  
9  
10

11 Friday, August 3, 2018

12 8:00 a.m. to 4:51 p.m.  
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14  
15

16 FDA White Oak Campus  
17 Building 31, the Great Room  
18 10903 New Hampshire Avenue  
19 Silver Spring, Maryland  
20  
21  
22

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9     Director

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2     Associate Director

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P R O C E E D I N G S

(8:00 a.m.)

**Call to Order**

**Introduction of Committee**

DR. BATEMAN: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. But I'd also like to identify the FDA press contact, Michael Felderbaum. If you're present, please stand; over there on the right.

My name is Brian Bateman. I'm the acting chairperson of the Drug Safety and Risk Management Advisory Committee, and I'll be chairing this meeting. I will now call today's Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee to order. We'll start by going around the table and introducing ourselves. We'll start with the FDA to my left and go around the table.

DR. RACOOSIN: Good morning. I'm Judy

1       Racoosin, deputy director for safety in the  
2       Division of Anesthesia, Analgesia, and Addiction  
3       Products.

4               DR. STAFFA: Good morning. I'm Judy Staff.  
5       I'm the associate director for public health  
6       initiatives in the Office of Surveillance and  
7       Epidemiology.

8               DR. MANZO: Good morning. My name is  
9       Claudia Manzo. I'm the director of the Office of  
10      Medication and Error Prevention and Risk Management  
11      in OSE.

12              DR. AUTH: Good morning. I'm Doris Auth,  
13      the associate director of the Division of Risk  
14      Management in OSE.

15              DR. LaCIVITA: Good morning. Cynthia  
16      LaCivita, director of the Division of Risk  
17      Management in OSE.

18              DR. ARFKEN: Good morning. Cynthia Arfken.  
19      I'm an epidemiologist and professor, Department of  
20      Psychiatry at Wayne State University in Detroit,  
21      Michigan.

22              DR. FRY: Hello. Michael Fry, pharmacist,

1 Providence Health and Services Oregon.

2 DR. KATZMAN: Hello. I'm professor of  
3 neurology at University of New Mexico. I direct  
4 the University of New Mexico Pain Center and  
5 Project ECHO Pain.

6 DR. BRANDON: Hello. My name is Paul  
7 Brandon. I'm an independent pharmacy owner out of  
8 Florence, Montana.

9 DR. LITMAN: Ron Litman. I'm a professor of  
10 anesthesiology and pediatrics at the University of  
11 Pennsylvania and the medical director of the  
12 Institute for Safe Medication Practice.

13 DR. KULLDORF: Good morning. My name is  
14 Martin Kulldorff. I'm a biostatistician in the  
15 Division of Pharmacoepidemiology at the Harvard  
16 Medical School and Brigham and Women's Hospital.

17 DR. BROWN: Rae Brown. I am a professor of  
18 anesthesiology and pediatrics at the University of  
19 Kentucky and a practicing pediatric  
20 anesthesiologist at Kentucky Children's Hospital.

21 DR. WANG: Yinghua Wang, designated federal  
22 officer.

1       Okay.

2               DR. BATEMAN:   Brian Bateman.   I'm an  
3       anesthesiologist at Brigham and Women's Hospital  
4       and associate professor at Harvard Medical School.

5               DR. WARHOLAK:   Good morning.   I'm Terri  
6       Warholak, and I'm a professor and assistant dean at  
7       the University of Arizona College of Pharmacy, and  
8       my specialty is quality and safety.

9               DR. MEISEL:   Steve Meisel, director of  
10       medication safety for Fairview Health Services in  
11       Minneapolis.

12              DR. JONIAK-GRANT:   Elizabeth Joniak-Grant.  
13       I'm the patient representative and a sociologist.  
14       I represent chronic pain, mostly arthritis and  
15       neuralgia, and I'm from the Raleigh/Durham, North  
16       Carolina area.

17              DR. HIGGINS:   Jennifer Higgins.   I'm the  
18       AADPAC acting consumer representative.

19              DR. HABEL:   Laurel Habel.   I'm an  
20       epidemiologist and associate director of cancer  
21       research at the Division of Research at Kaiser  
22       Permanente.

1 DR. GOUDRA: Basavana Goudra. I'm the  
2 anesthesiologist at the Hospital of the University  
3 of Pennsylvania and associate professor at Perelman  
4 School of Medicine.

5 DR. WARNER: I'm Margaret Warner. I'm an  
6 epidemiologist in the National Center for Health  
7 Statistics, Division of Vital Statistics and  
8 Mortality Statistics branch.

9 DR. SANDBRINK: Good morning. I'm Friedhelm  
10 Sandbrink. I'm a clinical associate professor at  
11 the Uniformed Services University in Bethesda,  
12 clinical assistant professor at George Washington  
13 University, and I'm the acting national program  
14 director for the Department of Veterans Affairs.  
15 I'm a neurologist and a pain physician.

16 DR. CRAIG: Good morning. I'm David Craig.  
17 I'm a pharmacist specialist at Moffitt Cancer  
18 Center in Tampa, Florida.

19 DR. NELSON: Good morning. I'm Lewis  
20 Nelson. I'm a professor of emergency medicine at  
21 Rutgers New Jersey Medical School in Newark, New  
22 Jersey, and a medical toxicologist, and I oversee

1 the New Jersey Poison Center.

2 DR. HERRING: Hello. Good morning. I'm Joe  
3 Herring. I'm a neurologist and associate vice  
4 president at Merck Research Laboratories and  
5 industry representative to the AADPAC.

6 DR. HERTZ: Good morning. I'm Sharon Hertz,  
7 director for the Division of Anesthesia, Analgesia,  
8 and Addiction Products.

9 DR. BATEMAN: And Dr. McCann is calling in.  
10 Dr. McCann, can you introduce yourself?

11 DR. McCANN: Yes. I'm Dr. McCann from  
12 Boston Children's Hospital, and I'm a pediatric  
13 anesthesiologist.

14 DR. BATEMAN: For topics such as those being  
15 discussed at today's meeting, there are often a  
16 variety of opinions, some of which are quite  
17 strongly held. Our goal is that today's meeting  
18 will be a fair and open forum for the discussion of  
19 these issues and that individuals can express their  
20 views without interruption. Thus, as a gentle  
21 reminder, individuals will be allowed to speak into  
22 the record only if recognized by the chairperson.

1 We look forward to a productive meeting.

2 In the spirit of the Federal Advisory  
3 Committee Act and the Government in the Sunshine  
4 Act, we ask at the advisory committee members take  
5 care that their conversations about the topics at  
6 hand take place in the open forum of the meeting.  
7 We are aware that members of the media are anxious  
8 to speak with the FDA about these proceedings.  
9 However, the FDA will refrain from discussing the  
10 details of this meeting with the media until after  
11 its conclusion.

12 Also, the committees are reminded to please  
13 refrain from discussing the meeting topic during  
14 breaks or lunch. Thank you.

15 I'll now pass it to Dr. Yinghua Wang, who  
16 will read the Conflict of Interest Statement.

17 **Conflict of Interest Statement**

18 DR. WANG: The Food and Drug Administration  
19 is convening today's joint meeting of the Drug  
20 Safety and Risk Management and Anesthetic and  
21 Analgesic Drug Products Advisory Committees under  
22 the authority of the Federal Advisory Committee Act

1 of 1972. With the exception of the industry  
2 representative, all members and temporary voting  
3 members of the committees are special government  
4 employees or regular federal employees from other  
5 agencies and our subject to federal conflict of  
6 interest laws and regulations.

7 The following information on the status of  
8 the committees' compliance with federal ethics and  
9 conflict of interest laws, covered by but not  
10 limited to those found at 18 USC, Section 208, is  
11 being provided to the participants in today's  
12 meeting and to the public. FDA has determined that  
13 members and temporary voting members of the  
14 committees are in compliance with federal ethics  
15 and conflict of interest laws.

16 Under 18 USC, Section 208, Congress has  
17 authorized FDA to grant waivers to special  
18 government employees and regular federal employees  
19 who have potential financial conflicts when it is  
20 determined that the agency's need for a special  
21 employee's services outweighs his or her potential  
22 financial conflict of interest, or when the



1 interest of a regular federal employee is not so  
2 substantial as to be deemed likely to affect the  
3 integrity of the services which the government may  
4 expect from the employee.

5 Related to the discussions of today's  
6 meeting, members and temporary voting members of  
7 the committees have been screened for potential  
8 financial conflict of interest of their own as well  
9 as those imputed to them, including those of their  
10 spouses or minor children, and for purposes of 18  
11 USC, Section 208, their employers. These interests  
12 may include investments; consulting; expert witness  
13 testimony; contract, grants, CRADAs; teaching,  
14 speaking, writing; patents and royalties; and  
15 primary employment.

16 Today's agenda involves discussion of  
17 results from assessment of the transmucosal  
18 immediate-release fentanyl, TIRF, medicines' risk  
19 evaluation and mitigation strategy, REMS, approved  
20 in December 2011. The TIRF REMS requires that  
21 healthcare providers who prescribe TIRF medicines  
22 for outpatient use are specially certified; that

1 pharmacies that dispense TIRF medicines for  
2 inpatient and outpatient use are specially  
3 certified; and that completion of the  
4 prescriber-patient agreement form occurs prior to  
5 dispensing TIRF medicines for outpatient use.

6 The agency will seek the committee's  
7 assessment as to whether this REMS was elements to  
8 assure safe use, ETASU, assures safe use; is not  
9 unduly burdensome to patient access to the drugs;  
10 and to the extent practicable, minimize the burden  
11 to the healthcare delivery system. The agency will  
12 also seek the committees' input on any possible  
13 modification to the TIRF REMS goals and  
14 requirements, as well as input on the adequacy of  
15 the evaluation conducted in the REMS assessment to  
16 determine whether the TIRF-REMS goals are being  
17 met.

18 This is a particular matters meeting during  
19 which general issues will be discussed. Based on  
20 the agenda for today's meeting and all financial  
21 interests reported by the committee members and  
22 temporary voting members, no conflict of interest

1       waivers have been issued in connection with this  
2       meeting. To ensure transparency, we encourage all  
3       standing committee members and temporary voting  
4       members to disclose any public statements that they  
5       have made concerning the topic at issue.

6               With respect to FDA's invited industry  
7       representative, we would like to disclose that  
8       Dr. W. Joseph Herring is participating in this  
9       meeting as a nonvoting industry representative  
10      acting on behalf of regulated industry.

11      Dr. Herring's role at this meeting is to represent  
12      industry in general and not any particular company.  
13      Dr. Herring is employed by Merck and Company.

14              We would like to remind members and  
15      temporary voting members that if the discussions  
16      involve any other topics not already on the agenda  
17      for which an FDA participant has a personal or  
18      imputed financial interest, the participants need  
19      to exclude themselves from such involvement, and  
20      their exclusion will be noted for the record. FDA  
21      encourages all other participants to advise the  
22      committees of any financial relationship that they

1       may have regarding the topic that could be affected  
2       by the committee's discussion. Thank you.

3               DR. BATEMAN: We will now proceed with the  
4       FDA's opening remarks from Dr. Sharon Hertz.

5                       **FDA Opening Remarks - Sharon Hertz**

6               DR. HERTZ: Good morning, Dr. Bateman,  
7       members of the Drug Safety and Risk Management  
8       Advisory Committee and the Anesthetic and Analgesic  
9       Drug Advisory Committee, and invited guests. I'd  
10      like to thank you all for coming to discuss this  
11      risk evaluation and mitigation strategy, which we  
12      call a REMS, for the transmucosal immediate-release  
13      fentanyl products, which we call TIRFs.

14              These products are indicated for a  
15      particular set of patients with a particular need.  
16      Patients are patients with breakthrough pain from  
17      cancer. Dr. Kilgore will discuss this indication  
18      and the characteristics of the TIRF products in her  
19      presentation.

20              Early on, the characteristics of these  
21      products that made them suitable for breakthrough  
22      cancer pain also created concern about the risk

1       that was potentially greater than for opioids in  
2       general. So TIRF products have been managed  
3       differently than other products starting with  
4       RiskMAP early on and then a class REMS once that  
5       tool became available.

6               Safety issues for these products have  
7       included the risk of pediatric exposure. This was  
8       a major concern with the first of this class, a  
9       sweet flavored lozenge on a stick. The products  
10      were studied in opioid-tolerant cancer patients on  
11      around-the-clock opioid therapy consistent with a  
12      population with substantial baseline pain and that  
13      also met the definition for breakthrough cancer  
14      pain.

15             All of the safety information was based on  
16      an opioid-tolerant population, and the REMS was  
17      considered one way to implement the safe use by  
18      educating prescribers and patients about the  
19      importance of being opioid tolerant and about the  
20      risks of overdose, particularly in those who were  
21      non-tolerant.

22             Further, in the midst of the growing wave of

1     prescription opioid analgesic abuse, these products  
2     could be looked upon favorably by abusers,  
3     including non-tolerant recreational abusers. Given  
4     the potency and the PK characteristics, we wanted  
5     to prevent abuse, addiction, and overdose or  
6     deaths.

7             In addition to these ongoing risks, the  
8     strength of the available dosage forms can be fatal  
9     to a child and remains a concern because of the  
10    potency of fentanyl and the strength of the  
11    individual dosages. Furthermore, the various brand  
12    name TIRF products are not therapeutically  
13    equivalent. They're not bioequivalent to one  
14    another, so patients cannot be switched from one  
15    product to another on a microgram-per-microgram  
16    basis, another important safety concern.

17            The TIRF REMS was put in place to try to  
18    minimize these concerns, but because of the unique  
19    need for these patients, a population of cancer  
20    patients with breakthrough pain, FDA tried to  
21    minimize the burden on providers and the healthcare  
22    system so as not to prevent access to patients who

1       need these products.

2               You'll hear this morning about the goals and  
3       the design of the TIRF REMS along with the results  
4       of the most current assessments of both its  
5       operational aspects as well as the medical outcomes  
6       of concern to us.

7               The operational aspects, the mechanics of  
8       the program, have been successfully implemented.  
9       However, we've noticed a marked decrease in  
10      utilization of TIRF products. Anecdotally, we hear  
11      that the TIRF REMS field is too burdensome to many  
12      clinicians. When clinicians opt not to participate  
13      in the TIRF REMS, we are concerned that access to  
14      the appropriate patients who may need these  
15      products may be limited.

16              One of our principle concerns from the  
17      assessment is the finding, based on claims data,  
18      that a substantial portion of patients' prescribed  
19      TIRFs are not opioid tolerant. We have  
20      independently conducted validation of the methods  
21      used in these kinds of claim studies to make sure  
22      this finding is real.

1           Dr. Jeffery's work, which you will hear  
2           about later today, suggests that it is. We have  
3           also asked the TRIF to conduct a validation study  
4           to reproduce this finding. The TRIF is the  
5           industry group who are responsible for this shared  
6           system REMS.

7           We have also looked in our own database of  
8           adverse events, known as FAERS, to see whether we  
9           have reports of serious adverse events or deaths  
10          among opioid non-tolerant patients who received  
11          TIRF products. But as you'll hear, the reports are  
12          not detailed enough to really inform us on this  
13          issue. So we've asked the TRIF to conduct studies  
14          to look at outcomes of patients prescribed TIRF who  
15          were not opioid tolerant, and these studies are  
16          ongoing.

17          We're also concerned about small but  
18          increasing rates of misuse and abuse of TIRFs in an  
19          environment where the rates of abuse of other  
20          analgesic opioids appear to be decreasing. Because  
21          TIRF products are not widely used and because of  
22          the small number of abuse reports from both poison



1 control centers and addiction treatment centers,  
2 interpretation of these findings are challenging.

3 New findings from FDA-sponsored research  
4 into the accuracy of reporting of specific drugs  
5 abused by those entering addiction treatment  
6 centers now cast out on the validity of treatment  
7 center findings for products with low volume like  
8 these TIRF, and these make the results even more  
9 difficult to interpret. Dr. Radin will share these  
10 late-breaking findings in her talk.

11 While the TIRF products are not widely used,  
12 only approximately about 5,000 patients nationwide,  
13 our mission is to ensure the safety of all  
14 patients. Our goal in discussing this program is  
15 to share and gather information to inform our  
16 actions to ensure the safety of cancer patients  
17 with breakthrough pain and others who are  
18 determined to have a clinical need for TIRF  
19 products.

20 We look forward to hearing your thoughts  
21 about this REMS and any ways we can improve it,  
22 particularly how we can measure key outcomes.

1 Thanks.

2 DR. BATEMAN: Thank you.

3 Both the Food and Drug  
4 Administration -- sorry.

5 DR. KILGORE: Are you ready for me to begin?

6 DR. BATEMAN: Please, go ahead, Dr. Kilgore.

7 **FDA Presentation - Elizabeth Kilgore**

8 DR. KILGORE: Thank you.

9 Good morning. My name is Elizabeth Kilgore.  
10 I'm a medical officer in the Division of  
11 Anesthesia, Analgesia, and Addiction Products.  
12 This morning, I will provide an overview of  
13 breakthrough pain in patients with cancer and  
14 provide a detailed presentation of the regulatory  
15 history of the approved TIRF products and REMS.

16 Breakthrough pain in patients with cancer  
17 has been defined in a number of ways. One of the  
18 earliest definitions is that by Portenoy, who  
19 defined breakthrough pain as a transitory  
20 exacerbation of pain that occurs on a background of  
21 otherwise stable persistent pain. Although the  
22 clinical presentation can vary, characteristics

1 often include quick onset, severe intensity, and  
2 relatively short duration.

3 There are various pharmacologic and  
4 nonpharmacologic interventions used to manage  
5 breakthrough pain in patients with cancer. TIRF  
6 medicines are one pharmacologic options available.  
7 Currently, there are 6 new drug application  
8 products and 4 abbreviated new drug application,  
9 ANDA products or generics, approved for treatment  
10 of breakthrough pain in cancer patients. All  
11 contain fentanyl, a potent opioid agonist that can  
12 cause respiratory depression in microgram  
13 quantities.

14 For this reason, the indication reflects the  
15 need for patients to be opioid tolerant, a  
16 physiological state in which patients are more  
17 tolerant to the CNS depression and respiratory  
18 depression associated with opioids. All are  
19 contraindicated in the management of pain in opioid  
20 non-tolerant patient.

21 TIRF medicines are formulated to provide  
22 rapid absorption for quick onset of action, usually

1 within 10 to 15 minutes or sooner, with short  
2 duration of effect, and are the only drugs  
3 specifically approved for the treatment of  
4 breakthrough pain in adult patients with cancer.

5 All opioids have serious safety risks to  
6 include respiratory depression, which could result  
7 in death, possible overdose, misuse and abuse.  
8 However, due to the type of formulations for the  
9 TIRFs, there are specific safety considerations,  
10 which include the products contain a high amount of  
11 fentanyl; there is concern for accidental ingestion  
12 by children; concern for improper patient  
13 selection, which includes prescription to and usage  
14 by opioid non-tolerant patients; and risk for  
15 diversion and abuse of TIRFs due to the  
16 formulations.

17 One major challenge that the FDA faces with  
18 this class of medicines is how to find the optimal  
19 strategy to balance the patient's need for cancer  
20 breakthrough pain management versus the potential  
21 public health risks associated with availability of  
22 a potent opioid analgesic. The population at

1       greatest risk for adverse effects may not be the  
2       population that has the greatest need for these  
3       products. Because of the challenges related to  
4       TIRF medicines, they have been discussed at two  
5       prior advisory committee meetings. Over the next  
6       few slides, I will walk through the regulatory  
7       history of the TIRF medications.

8               The first formulation of oral transmucosal  
9       fentanyl citrate -- trade name, Oralet -- was  
10      approved in 1993 for preoperative sedation in  
11      children in a monitored setting. The product was  
12      formulated as a lozenge on a stick so that it would  
13      be acceptable to the pediatric population.

14             After approval, it became evident that  
15      opioid-naive children who received it could not  
16      tolerate the associated adverse effects of nausea  
17      and vomiting. The application holders ceased  
18      marketing of Oralet in 2001, and more recently  
19      withdrew the NDA in 2016. Since Oralet is no  
20      longer marketed, it will not be discussed further  
21      as it does not include it in the TIRF REMS.

22             This slide provides an overview of the

1 select regulatory history of the TIRF REMS that I  
2 will discuss in detail in the coming slides. The  
3 timeline begins with 1997, when Actiq's fentanyl  
4 lozenge, the second TIRF product, new application  
5 was submitted, and ALSDAC meeting was held, and  
6 goes through 2012 when the class-wide TIRF REMS was  
7 launched.

8 In September 1997, the ALSDAC meeting was  
9 held regarding the Actiq application to discuss the  
10 challenge of balancing the risk versus the benefit  
11 of this product. The committee voted unanimously  
12 that there should be a way found to make Actiq  
13 available to those patients who would potentially  
14 benefit from it while managing the potential risk  
15 to public health.

16 In 1998, Actiq was approved with a risk  
17 management program. The primary components of  
18 Actiq's risk management program emphasized  
19 labeling, child resistant design features,  
20 educational programs, and interventions at the  
21 point of dispensing.

22 Following the approval of Actiq in 1998, no

1 new TIRF products were approved until 2006, when  
2 Fentora buccal tablet was approved with a risk  
3 minimization action plan or RiskMAP. The primary  
4 components of Fentora's RiskMAP emphasized the  
5 following: an education component, a surveillance  
6 system, and a plan to monitor and evaluate  
7 incidence of use of Fentora by opioid non-tolerant  
8 individuals' misuse and accidental exposure.

9 With the FDA Amendments Act of 2007, the FDA  
10 was granted the authority to require sponsors to  
11 develop and comply with REMS programs if it was  
12 determined necessary to ensure the benefits  
13 outweigh the risk.

14 Prior to 2007, FDA did not have explicit  
15 authority to require a REMS when necessary. Also  
16 in 2007, Fentora submitted an efficacy supplement  
17 for the proposed indication of breakthrough pain in  
18 non-cancer patients with chronic pain. On May 6,  
19 2008, this supplement was discussed at a joint  
20 ALSDAC and DSaRM advisory committee meeting.

21 At the 2008 AC meeting, one key focus was on  
22 Fentora's RiskMAP failures. Some of the key

1 deficiencies included failure to ensure proper  
2 patient selection for patients with cancer or  
3 patients that were opioid tolerant; failure to  
4 provide adequate education of prescribers and  
5 dispensers; there were reports of patient deaths  
6 after being treated for migraine headache and  
7 chronic low back pain; increasing numbers of opioid  
8 non-tolerant patients were being prescribed  
9 Fentora; and medication errors such as improper  
10 dose titration, improper conversion from an  
11 improper substitution for Actiq.

12           The committee voted not to expand Fentora's  
13 indication. Following the advisory committee  
14 meeting, the agency determined that a REMS was  
15 necessary to assure the safe use of oral  
16 transmucosal fentanyl products.

17           In 2009, FDA approved Onsolis buccal film  
18 with an individual REMS with elements to assure  
19 safe use. The next speaker will provide more  
20 detail regarding the components of the elements to  
21 assure safe use.

22           In October 2010, the agency met with the



1 application holders referred to as the TIRF REMS  
2 industry group, or TRIG, of the TIRF medicines and  
3 requested they work together to develop shared  
4 system REMS for all TIRF medicines to minimize the  
5 burden to healthcare providers and patients.

6 In 2011, FDA approved Abstral sublingual  
7 tablet and Lazanda nasal spray with their  
8 individual REMS with elements to assure safe use.  
9 Also on December 28, 2011, the TIRF REMS was  
10 approved and includes Actiq, Fentora, Onsolis,  
11 Abstral, Lazanda, and generic equivalence of Actiq,  
12 Fentora and Abstral. Subsys sublingual spray  
13 joined the TIRF REMS on January 4, 2012 with its  
14 approval. The TIRF REMS, also referred to as the  
15 TIRF REMS Access Program, was launched on March 12,  
16 2012.

17 In conclusion, this table provides a summary  
18 of the approved new drug applications and generic  
19 for TIRF medicines. As seen in the table, there  
20 are 6 NDA products. These products are not  
21 equivalent and are not to be substituted for each  
22 other. Thank you.

1 DR. BATEMAN: The next presentation is from  
2 the FDA, Dr. LaCivita.

3 **FDA Presentation - Cynthia LaCivita**

4 DR. LaCIVITA: Good morning. My name is  
5 Cynthia LaCivita, and I'm the director of the  
6 Division of Risk Management. Today I'm going to  
7 provide an overview of REMS authorities, the TIRF  
8 REMS program, and the TIRF REMS assessments.

9 A risk evaluation and mitigation strategy,  
10 or a REMS, is a risk management plan that utilizes  
11 strategies beyond labeling to ensure that the  
12 benefits of a drug outweigh the risks. The FDA  
13 Amendments Act of 2007 authorized FDA to require a  
14 sponsor to develop and comply with REMS programs if  
15 determined to be necessary to ensure the benefits  
16 outweigh the risks.

17 REMS are designed to achieve specific goals  
18 and to mitigate risks associated with the use of a  
19 drug. The agency has the authority to require REMS  
20 either pre-approval or post-approval. A REMS may  
21 include a medication guide or patient package  
22 insert, a communication plan, elements to assure

1 safe use, or an implementation system. A REMS must  
2 include a timetable for submission of assessment of  
3 the REMS.

4 Elements to assure safe use are  
5 interventions or other actions healthcare providers  
6 may need to execute prior to prescribing or  
7 dispensing a drug to a patient. They provide safe  
8 access to patients with drugs with known serious  
9 risks that would otherwise not be approved or would  
10 be withdrawn.

11 Elements to assure safe use can include  
12 certification and specialized training of  
13 healthcare providers who prescribe the drugs;  
14 certification of pharmacies or other dispensers of  
15 the drugs; dispensing or administration of the drug  
16 in limited settings such as hospitals, but the drug  
17 is dispensed/administered only with a safe-use  
18 condition. An example would be a pregnancy test in  
19 the case where the product is a teratogen.

20 Each patient using the drug is subject to  
21 certain monitoring or the enrollment of a treated  
22 patient in a registry. The use of these elements

1 are not mutually exclusive, and they often need to  
2 be combined to achieve the goals of the REMS.

3 Elements to assure safe use should be  
4 commensurate with specific serious risk listed in  
5 the labeling of the drug. They should not be  
6 unduly burdensome on patient access to drugs, and  
7 considering in particular patients with serious or  
8 life-threatening conditions and patients who may  
9 have difficulty accessing healthcare. They should  
10 be similar to other products with elements to  
11 assure safe use that have similar serious risks,  
12 and they should be designed to be compatible with  
13 the healthcare delivery system.

14 Next, I'll provide a brief overview of the  
15 TIRF REMS program. In October of 2010, the agency  
16 requested that the TIRF sponsors work together to  
17 develop a shared-system REMS. A shared-system REMS  
18 may encompass multiple drug products and is  
19 developed and implemented jointly by at least two  
20 or more applicants. It includes a single REMS  
21 document, REMS materials, and REMS supporting  
22 document across all products. It has the potential

1 to minimize the burden to healthcare providers and  
2 patients by eliminating the need for them to  
3 certify or enroll in a separate program for each  
4 product.

5 The initial approval of the TIRF REMS was  
6 December of 2011. It was fully implemented in  
7 March of 2012. This program is also referred to as  
8 the TIRF REMS Access Program. Several  
9 modifications have occurred to the TIRF REMS since  
10 initial approval. I'll cover one in the future  
11 slides.

12 The goals and the objectives of the TIRF  
13 REMS are to mitigate the risk of misuse, abuse,  
14 addiction, overdose, and serious complications due  
15 to medication errors; prescribing and dispensing  
16 TIRF REMS medicines only to appropriate patients,  
17 which includes use in only opioid-tolerant  
18 patients; preventing inappropriate conversions  
19 between TIRF medicines; preventing accidental  
20 exposure to children and for others whom it was not  
21 prescribed; as well as educating prescribers,  
22 pharmacists, and patients on the potential for

1 misuse, abuse, addiction, and overdose with these  
2 products.

3 The TIRF REMS has three key components:  
4 prescriber certification when the prescriptions are  
5 intended for outpatient use; pharmacy certification  
6 for both outpatient and inpatient dispensing  
7 settings; and a patient-prescriber agreement form  
8 when the prescription is intended for outpatient  
9 use.

10 Prescribers must certify when the  
11 prescription is intended for outpatient use. They  
12 complete the required education and must  
13 successfully complete the knowledge assessment.  
14 They enroll initially and then re-enroll every two  
15 years. They must complete a patient-prescriber  
16 agreement form for each patient with their first  
17 prescription, and then every two years.

18 Outpatient pharmacies are also required to  
19 certify. They do this through a designated  
20 authorized representative who enrolls on the  
21 pharmacy's behalf. The authorized representative  
22 must complete the required education and

1       successfully complete the knowledge assessment,  
2       enroll initially and every two years and ensure  
3       that all staff are trained. Prior to dispensing in  
4       the outpatient setting, pharmacy staff must verify  
5       that the prescriber is certified and the  
6       patient-prescriber agreement form was received  
7       within 10 days of the first prescription.

8               Inpatient pharmacies must also certify, and  
9       they also use a designated authorized  
10       representative which enrolls on their behalf. The  
11       authorized representative also completes the  
12       required education and the knowledge assessment; is  
13       required to enroll initially in every two years;  
14       ensures that all staff are trained on the REMS; and  
15       they must establish order sets, protocols, or other  
16       measures to help ensure appropriate patient  
17       selection and compliance with the REMS.

18               A key intervention of the TIRF REMS is  
19       education. The education for prescribers and  
20       patients covers the following topics: increased  
21       risk of misuse, abuse, respiratory depression, and  
22       overdose, whether it's accidental or intentional;

1       that these products should only be prescribed to  
2       patients who are already receiving and are tolerant  
3       to around-the-clock opioid therapy; they are  
4       indicated for breakthrough pain in cancer patients  
5       and should not be used in the treatment of acute or  
6       post-operative pain; and also there was a potential  
7       for accidental exposure, particularly in children.

8               The patient-prescriber agreement form is  
9       required when TIRF medicines are prescribed for  
10       outpatient use. Patients are passively enrolled  
11       with the first prescription. The form must be  
12       received by the REMS program within 10 days of when  
13       the first prescription is filled.

14              The REMS has undergone several modifications  
15       since its approval. The prescriber attestations on  
16       the patient-prescriber agreement form, as initially  
17       approved in December of 2011, were, "my patient is  
18       currently receiving around-the-clock opioids and  
19       has been for at least one week," "my patient is  
20       opioid tolerant," and patients who are considered  
21       opioid tolerant are those who are readily taking at  
22       least the following, as listed here on the slide.



1           In November of 2013, the prescriber  
2       attestations on the form were revised. They now  
3       read, "I understand the TIRF medicines are  
4       indicated only for the management of breakthrough  
5       pain in patients with cancer who were already  
6       receiving and who are tolerant to around-the-clock  
7       opioid therapy for their persistent pain.

8           "I understand that TIRF medicines are  
9       contraindicated for use in opioid non-tolerant  
10      patients. I know that fatal overdose can occur at  
11      any dose." And lastly, "I understand that patients  
12      who are considered opioid tolerant are those who  
13      are regularly taking at least the following," as  
14      listed here on the slide.

15           Next, I'll move on to the TIRF REMS  
16      assessment. The TIRF sponsors are required to  
17      submit assessment reports. The timetable for the  
18      submission of the assessment requires that the  
19      sponsor submit the REMS assessment reports at 6 and  
20      12 months from the date of initial approval and  
21      then annually thereafter.

22           The agency has received a total of 7 reports

1 from the members of the TIRF REMS that span the  
2 time frame from 6 months to 72 months. The 60th  
3 and the 72-month assessment are the topic of  
4 today's discussion. The sponsors submit a single  
5 assessment report with aggregate data involving all  
6 the TIRF medicines.

7 The TIRF assessment plan includes 6 metrics,  
8 enrollment statistics and utilization data;  
9 dispensing data such as authorizations or  
10 rejections that have occurred through the TIRF  
11 REMS; information about the program infrastructure;  
12 and program noncompliance and any corrective  
13 actions that were taken.

14 The surveillance data focuses on addiction,  
15 overdose, death, pediatric exposures, and opioid  
16 non tolerance. And there are stakeholder surveys  
17 for prescribers, pharmacists, and patients to  
18 assess their knowledge of the risks, safe use, and  
19 storage conditions.

20 I'd like to end with an overview of today's  
21 agenda. My presentation will be followed by the  
22 industry presentations with time for clarifying

1 questions, followed by FDA presentations, and then  
2 lunch. We have two guest speakers here today,  
3 guest presentations, the Yale University-Mayo CERSI  
4 will be presenting and also Centers for Medicare  
5 and Medicaid Services. The open public hearing is  
6 at 1:30, and then we will provide a charge to the  
7 committees, and then we look forward to discussion.

8 I want to thank you for your time today. We  
9 appreciate it, and we're looking forward to a very  
10 thoughtful discussion. Thank you.

11 DR. BATEMAN: Thank you.

12 Both the Food and Drug Administration and  
13 the public believe in a transparent process for  
14 information-gathering and decision-making. To  
15 ensure such transparency at the advisory committee  
16 meeting, FDA believes that it is important to  
17 understand the context of an individual's  
18 presentation.

19 For this reason, FDA encourages all  
20 participants, including the applicant's nonemployee  
21 presenters, to advise the committee of any  
22 financial relationships that they may have with the

1 applicant such as consulting fees, travel expenses,  
2 honoraria, and interest in a sponsor, including  
3 equity interests and those based upon the outcome  
4 of the meeting.

5 Likewise, FDA encourages you at the  
6 beginning of your presentations to advise the  
7 committee if you have any such financial  
8 relationships. If you choose not to address this  
9 issue of financial relationships at the beginning  
10 of your presentation, it will not preclude you from  
11 speaking.

12 We'll now proceed with presentations from  
13 the TIRF REMS industry group, TRIG.

14 **Industry Presentation - Stephen Sherman**

15 MR. SHERMAN: Good morning, members of the  
16 committee. Thank you for having us. My name is  
17 Steve Sherman, and I'm representing the TIRF REMS  
18 industry group, or the TRIG, as the moderator for  
19 today's meeting. While there are numerous options  
20 to treat pain, there is only one class of products  
21 specifically approved to treat breakthrough cancer  
22 pain, and those are the TIRFs. Other treatments

1 generally do not either have a fast enough onset or  
2 they last far too long. Thus, it is imperative  
3 that breakthrough cancer pain patients have access  
4 to TIRFs to treat this debilitating condition  
5 through the TIRF REMS Access Program.

6 As Dr. Kilgore went through the history of  
7 the TIRFs, they actually started with Actiq in a  
8 risk management plan, and 6 products were approved  
9 with the RiskMAP, than a REMS, and then the TIRF  
10 REMS was introduced in 2012.

11 The agency had determined in 2010, though,  
12 to minimize the burden on healthcare providers and  
13 patients, the TIRF should engage in a single-shared  
14 system, and that's the TIRF REMS. A notification  
15 letter was sent out in November of 2010 to all the  
16 manufacturers, and the TIRF REMS was the first  
17 program to cover an entire category of opioids.

18 As the agency noted, if the perceived effort  
19 to complete the REMS outweighs the benefits of  
20 prescribing the medicine, this could possibly  
21 prompt physicians to refuse to prescribe drugs  
22 covered by the REMS at all. We need to ensure that

1 the TIRF REMS does not become a barrier to patient  
2 access. It was designed to ensure that the  
3 benefits of the TIRFs outweigh the risks associated  
4 with their use.

5 As mentioned by Dr. Kilgore, the goals of  
6 the program are to reduce the risk of misuse,  
7 abuse, addiction, overdose, and serious  
8 complications due to medication errors. To achieve  
9 these goals, the TIRF REMS has to strike a  
10 strategic balance between managing the risk  
11 associated with the use of the TIRF without unduly  
12 burdening healthcare prescribers and denying access  
13 to these important products to cancer patients to  
14 alleviate this debilitating, life-limiting  
15 condition.

16 As also mentioned, the elements of the TIRF  
17 REMS were presented and will be discussed in more  
18 detail in a later section. The TIRF REMS industry  
19 group, or the TRIG, as is known, is comprised of 8  
20 companies on the slide. We also have three  
21 partners that help us administer and implement the  
22 TIRF REMS, and this is really the group responsible

1 for administering the TIRF REMS Access Program.

2 As will be discussed in more detail later,  
3 there were unmet needs for patients to control  
4 pain, so the TIRFs were actually developed, and  
5 these products are the ones that are currently on  
6 the market.

7 The TIRF REMS Access Program was designed  
8 with and approved by the FDA. Based on the results  
9 of the annual assessment reports that we submit,  
10 the TRIG and the agency work together to modify the  
11 program to ensure that it continues to meet its  
12 goals.

13 The program is continuously monitored and  
14 modified when and where appropriate. Since its  
15 inception, the TRIG has submitted 7 assessment  
16 reports. In addition to those, we've also  
17 submitted supplemental reports and updates to  
18 address either FDA recommendations or inquiries in  
19 response to these annual assessment reports. The  
20 TRIG also have individually submitted  
21 product-specific opioid tolerance analysis to the  
22 FDA in June of 2017 as agreed to by the FDA.

1           As this information on this slide  
2 illustrates, the TIRF REMS program is dynamic and  
3 not static. From its inception, the TRIG and the  
4 FDA have worked together to modify the program to  
5 continuously improve the likelihood of achieving  
6 its goals.

7           The TIRF REMS Access Program was designed to  
8 educate healthcare prescribers, pharmacists, and  
9 patients about the benefits and risks associated  
10 with the use of TIRFs and to identify appropriate  
11 patients. There are many activities currently  
12 ongoing to reinforce healthcare providers the  
13 appropriate use of TIRFs.

14           The agenda for our presentation is as  
15 follows. Dr. Joseph Pergolizzi will provide  
16 insight into breakthrough cancer pain and the  
17 public health impact of the TIRF medicines.

18           Kyle Irwin will provide an overview of the  
19 TIRF REMS Access Program and its design as a closed  
20 system.

21           Dr. Annette Stemhagen will review the  
22 results of the assessments of the TIRF REMS Access



1 Program, demonstrating that the accumulated data  
2 support that the REMS system is working.

3 Dr. Richard Dart will discuss the RADARS  
4 data, which supports the TIRF REMS data, and then  
5 Dr. Dean Mariano will provide an assessment of the  
6 benefit and risk of the TIRF REMS Access Program.  
7 And then I'll return to review the planned changes  
8 to the program and proposed action items with our  
9 conclusions.

10 Dr. Pergolizzi?

11 **Industry Presentation - Joseph Pergolizzi**

12 DR. PERGOLIZZI: Thank you, Steve.

13 I am Joe Pergolizzi, senior partner and  
14 director of research at Naples Anesthesia and Pain  
15 Associates in Naples, Florida. I'm an  
16 anesthesiologist pain medicine physician who has  
17 been TIRF REMS certified since its inception. I am  
18 being compensated by the TRIG for my attendance at  
19 this meeting, but I have no financial interest in  
20 the outcome of today's meeting.

21 I spent 20 years of my life developing and  
22 educating on analgesics and have a long-standing

1 professional interest in treating cancer pain,  
2 including breakthrough cancer pain episodes, so I  
3 am appreciative of the opportunity to speak with  
4 you today. This is a constant battle with the use  
5 of any opioid pain medications between the benefits  
6 that a patient may receive and the risk for that  
7 individual patient.

8 From a public health perspective, a similar  
9 balance exists between the societal benefits of  
10 managing pain effectively and the societal harms  
11 associated with opioid use.

12 In 2015, there were over 15 million patients  
13 living with cancer in the United States, and most  
14 of them will experience pain related to their  
15 cancer. Cancer pain is the most feared symptom of  
16 cancer and usually moderate to severe in intensity,  
17 particularly in later stages. Cancer pain may be  
18 caused by cancer itself and diagnostic procedures  
19 or treatments. It falls into four categories:  
20 somatic, visceral, neuropathic, and mixed. And  
21 cancer pain is inversely correlated with quality of  
22 life. It can be debilitating and have a dramatic

1       impact on the lives of patients and their families.

2               As a physician, we face a moral imperative  
3       to we relieve cancer pain, and it is important to  
4       distinguish cancer pain from non-cancer pain. Most  
5       cancer pain requires around-the-clock opioid pain  
6       medications, but for many patients, these are  
7       inadequate to manage all of their cancer pain. It's  
8       important that we address all aspects of cancer  
9       pain to the best of our abilities.

10              Persistent cancer pain is defined as a  
11       moderate to severe pain that lasts greater than 12  
12       hours per day. It's typically managed with  
13       around-the-clock opioids as part of a multimodal  
14       treatment plan. Around the clock means that the  
15       opioids are administered at regularly scheduled  
16       intervals throughout the day. While  
17       around-the-clock opioids are generally effective in  
18       managing persistent cancer pain, they do not  
19       prevent the occurrence of intense pain episodes  
20       that break through the background of opioid  
21       therapy.

22              Breakthrough cancer pain is intense,

1 episodic pain that typically has a rapid onset and  
2 a short duration. It can be caused by cancer  
3 itself, but also by diagnostic procedures,  
4 treatment, or activity such as physical therapy.  
5 Breakthrough cancer pain experienced by some  
6 patients is episodic and unpredictable.

7 The median time to peak pain intensity is 10  
8 minutes, but it can be immediate or develop over a  
9 longer time as long as an hour. It typically lasts  
10 60 to 90 minutes. It occurs as frequently as  
11 7 times per day and is often very intense, but can  
12 range from moderate to severe. Approximately  
13 two-thirds of the cancer patients will experience  
14 breakthrough cancer pain.

15 Breakthrough cancer pain can have a  
16 devastating impact on the lives of patients and  
17 their families, affecting every area of their  
18 lives. Breakthrough cancer pain may limit  
19 activities of daily living such as sleep, work, and  
20 self-care and constrain relationships and impede  
21 social activities.

22 The net effect can be a reduction in

1       enjoyment of life, reflecting substantial  
2       disability and decreased physical function along  
3       with psychological impact. Patients can experience  
4       anxiety and depression. The nature of the pain can  
5       generate a feeling of lack of control over one's  
6       life and a sense of isolation. Patients with  
7       breakthrough cancer pain have 5 times greater  
8       healthcare utilization from related  
9       hospitalizations, emergency room visits, and  
10      doctors' visits.

11               The effective management of cancer pain is  
12      associated with improved quality of life and  
13      prolong survival. It is important to match the  
14      appropriate therapy to the type of cancer pain.  
15      The TIRF products are best suited for breakthrough  
16      cancer pain because they have the shortest onset of  
17      action and the shortest effective duration.

18               Short-acting opioids are better suited for  
19      pain that does not require a fast onset of action  
20      because they can require up to 90 minutes to the  
21      effect of pain and last up to 6 hours. So they may  
22      not be optimal for treating breakthrough cancer

1 pain.

2           Some physicians will use short-acting  
3 opioids for around-the-clock pain management to  
4 treat the underlying persistent cancer pain.  
5 Around-the-clock, short-acting opioids will  
6 typically require more frequent dosing than the  
7 longer-acting medications, which have effective  
8 durations of analgesia between 8 to 72 hours, but  
9 also a much lower onset of action as high as 12  
10 hours. All of these factors should be considered  
11 in an effective management of cancer pain, keeping  
12 in mind the total opioid exposure.

13           The blue line area of this graph represents  
14 total opioid exposure and a schematic  
15 representation of the area under the curve of the  
16 blue line depicting the around-the-clock opioid  
17 therapy. The red line represents the pain  
18 intensity of breakthrough cancer pain that is not  
19 adequately managed by the around-the-clock regimen.

20           Around-the-clock opioids are the treatment  
21 of choice for chronic, persistent, moderate to  
22 severe cancer pain. However, they are not optimal

1       therapy for episodes of breakthrough cancer pain.  
2       Increasing the dose of the around-the-clock therapy  
3       in order to manage the breakthrough cancer pain  
4       typically results in overtreatment.

5               Here, the total exposure of opioid is more  
6       than doubled to manage the breakthrough cancer  
7       pain. This is substantially more opioid than would  
8       be necessary because here breakthrough cancer pain  
9       is brief and episodic. Increasing the dose of the  
10       around the clock and the manner needlessly  
11       increases the total opioid exposure and the risk of  
12       an adverse event such as respiratory depression or  
13       sedation.

14              Treatment of the breakthrough cancer pain  
15       with oral short-acting opioids can take 30 to 90  
16       minutes to produce an analgesic effect, which is  
17       too long, as represented by the yellow lines, and  
18       many miss the entire episode of breakthrough cancer  
19       pain. Furthermore, the peak analgesic effect may  
20       be insufficient to manage the intensity of the  
21       breakthrough cancer pain.

22              The analgesic effect can last 3 to 6 hours,

1 extending a long path of duration of the episode,  
2 exposing the patient to a total opioid load that  
3 they did not require to treat breakthrough cancer  
4 pain episodes, which would lead to adverse events  
5 while still not managing the pain. One risk of  
6 this approach is that the patient could re-dose  
7 while waiting for the short-acting opioid to  
8 produce an analgesic effect.

9 In this schematic representation, the  
10 patient has taken a second dose of a short-acting  
11 opioid 30 minutes after the original dose as seen  
12 around the 12-hour time mark. This re-dosing can  
13 occur when a patient has not experienced adequate  
14 pain relief in a timely manner.

15 It results in a higher peak analgesic effect  
16 that may be sufficient to address the intensity of  
17 the breakthrough cancer pain, but it still occurs  
18 long after the onset of pain and can persist for  
19 hours after the pain has subsided. This is a  
20 dangerous scenario of opioid misuse and can result  
21 in serious adverse events such as respiratory  
22 depression and sedation and could require medical



1 intervention.

2 The TIRF medications represented here in the  
3 green lines are designed precisely to address the  
4 needs of patients with cancer breakthrough pain.  
5 They match the onset, peak intensity, and duration  
6 of the pain. In this way, they can effectively  
7 manage the pain while minimizing the total opioid  
8 exposure compared to the use of long-acting or  
9 short-acting opioids to treat this type of pain.

10 TIRF medications are well suited for the  
11 management of breakthrough cancer pain. The routes  
12 of administration enable rapid absorption and onset  
13 of action. The peak effect can coincide with the  
14 peak pain intensity. The short duration of action  
15 can match the duration of pain. The high potency  
16 is also appropriate for the intensity of  
17 breakthrough cancer pain.

18 They can be self-administered or  
19 administered by caregivers without the need for  
20 healthcare professional involvement or the use of  
21 needles. They do not require swallowing, which is  
22 very important for patients with dysphasia or those

1 experiencing nausea and vomiting, both of which are  
2 common in cancer patients. The route of  
3 administration avoids exposure variability to the  
4 GI tract and first-pass metabolism.

5 Despite the effectiveness and availability  
6 of TIRF medications, most patients do not receive  
7 them and do not have adequate management of their  
8 breakthrough cancer pain. Multiple publications  
9 report that breakthrough cancer pain either goes  
10 completely untreated in about one third of the  
11 patients whose only prescribed treatment is rest.

12 It is undertreated in another third of the  
13 patients who receive non-opioid pain medication.  
14 Patients who receive opioids are mostly getting  
15 morphine, which has too slow an onset of action and  
16 insufficient potency to manage breakthrough cancer  
17 pain. Only a quarter of the patients in one study  
18 reported that they had an effective medication that  
19 worked every time to manage their breakthrough  
20 cancer pain.

21 I see in my own practice when patients are  
22 referred to me having previously endured

1       undertreated or untreated breakthrough cancer pain.  
2       Fortunately, we have the right medications, but  
3       patients in some settings never receive adequate  
4       management of their pain. The results is needless  
5       suffering and the potential for misuse of other  
6       opioid medications to manage breakthrough cancer  
7       pain.

8               There are multiple barriers to effective  
9       pain management. Some of the barriers are  
10      societal. People have negative feelings and  
11      perceptions about reporting cancer pain and using  
12      pain medications, especially opioids. They're  
13      afraid of addiction and side effects. Their family  
14      members may share and express similar fears.

15             Additionally, there are some patients who  
16      may not have the capacity to adequately express  
17      their pain or access to the medical resources they  
18      need to manage it. Many healthcare provisions are  
19      not proficient in pain management and may not have  
20      time or ability to adequately assess the patient's  
21      pain profile.

22             Healthcare professionals are also not immune

1 to the same societal concerns about pain and pain  
2 management and may themselves be reluctant to  
3 prescribe opioids. In addition, some may have  
4 particular concerns about fentanyl and TIRF  
5 medications, especially with all the recent  
6 negative reports in the press, as well as the  
7 increasing burden of regulatory affects on opioid  
8 prescribing. Finally, the healthcare system and  
9 payers may present additional barriers that reduce  
10 access to opioids.

11 Well, we're seeing over time, in the recent  
12 years, that there has been a consistent decline in  
13 the number of prescriptions of TIRF medications  
14 even while we know that there are more patients  
15 being diagnosed with cancer and living longer with  
16 cancer and cancer pain. Even before these  
17 decreases, there were clearly too few prescriptions  
18 for the TIRF products relative to the number of  
19 growing people living with cancer pain.

20 As a physician who has dedicated his life to  
21 pain management, I see there is a huge problem that  
22 results in needless suffering that we know how to

1       alleviate. There was a stark contrast between the  
2       U.S. and Western Europe, where there has been a  
3       higher total number of prescriptions even though  
4       the population sizes are similar and steadily  
5       increase in prescriptions over the same period of  
6       the greatest decrease in the United States.

7               There are substantial public health benefits  
8       associated with TIRF products and the TIRF REMS  
9       Access Program. The products effectively managed  
10      breakthrough cancer pain. This is very important  
11      to the lives of patients and their families,  
12      helping them maintain daily functioning and ability  
13      to contribute to society.

14             The effective use of TIRF products to manage  
15      breakthrough cancer pain can minimize the risk of  
16      associated an unwanted dose increases of the  
17      around-the-clock opioid therapy or from the risk of  
18      misuse of serial dosing outside the recommended  
19      dosing intervals of other opioids due to the delay  
20      of onset of action. Further, their use can result  
21      in lower and shorter exposure of other opioids  
22      compared with attempts to manage breakthrough

1 cancer pain with higher doses of around-the-clock  
2 opioids or as-needed use of short acting opioids.

3 The TIRF REMS Access Program has public  
4 health benefits, too. It was the first opioids  
5 REMS and has a rigorous program that provides for  
6 controlled prescribing, distribution, and  
7 dispensing. The program enables centralized  
8 tracking of the participants in the REMS because it  
9 requires mandatory participation from prescribers,  
10 physicians, and patients.

11 It also requires that all three groups  
12 undergo mandatory education with specific  
13 certification for pharmacists and prescribers who  
14 must pass a test to obtain certification. The  
15 entire program delivers important public health  
16 benefits by mitigating the risks associated with  
17 opioid products while maintaining access for  
18 appropriate patients who need them.

19 While all opioids have risk of abuse,  
20 misuse, diversion, overdose, and death, the  
21 utilization of TIRF products, which have only one  
22 indication and a controlled system of distribution,

1 is far lower than other prescription opioid  
2 products. In 2017, there were over \$196 million  
3 prescriptions dispensed for opioids in the U.S. In  
4 the same period, the total dispensing of fentanyl  
5 was 3.8 million prescriptions of which 64,000 were  
6 prescribed for TIRF products.

7 The non-TIRF fentanyl products, IV and  
8 transdermal fentanyl, account for 98.3 percent of  
9 the fentanyl prescriptions in the United States or  
10 about 3.8 million prescriptions. According to the  
11 2017 National Drug Threat Assessment from the Drug  
12 Enforcement Administration, small amounts are  
13 diverted from healthcare facilities typically for  
14 personal use or street sale. Abusers can extract  
15 fentanyl from patches to smoker, ingest extracted  
16 fentanyl solution, and IV products can be injected.

17 While these forms of abuse do occur, they  
18 are a small factor in the opioid crisis. TIRF  
19 medications are even a smaller factor. The TIRF  
20 products have potential public health related risks  
21 to fentanyl, which is a highly potent opioid with a  
22 high risk of overdose and death. Fentanyl itself

1 is highly desirable for abuse. However, the TIRF  
2 products are hard to obtain and are only available  
3 in microgram doses. They have shown a low rate of  
4 utilization and a low rate of diversion and abuse.  
5 As a result, they are only a small factor in the  
6 larger opioid crisis.

7 By contrast, illicitly manufactured fentanyl  
8 is much more prevalent for abuse. According to the  
9 DEA, illicitly manufactured fentanyl was  
10 responsible for the U.S. fentanyl problem. IMF  
11 comes from vast global market. Most of the  
12 production is in China. They produce fentanyl and  
13 fentanyl derivatives along with fentanyl-laced  
14 counterfeit look-alike prescription opioids.

15 Illicitly manufactured fentanyl is also a  
16 frequent additive to street drugs. Because  
17 fentanyl is so potent and may be included in street  
18 drugs without control of the amounts or indication  
19 to users, it is frequently involved in ER visits,  
20 overdoses, and deaths. Fentanyl is easily  
21 purchased online through the dark web in the global  
22 marketplace with simple electronic payment



1 cryptocurrency and easily shifting with the use of  
2 the U.S. Postal Service and other international  
3 ships. Illicitly manufactured fentanyl is a major  
4 contributor to the U.S. opioid crisis.

5 The TIRF products effectively manage  
6 breakthrough cancer pain with a public health  
7 benefit in and of itself, and also has benefits  
8 relative to the use of other opioid products that  
9 could be used to treat breakthrough cancer pain in  
10 terms of providing a lower and shorter total opioid  
11 exposure.

12 The TIRF REMS Access Program has public  
13 health benefits in terms of providing access to  
14 pain medications with controlled prescribing,  
15 distribution, and dispensing, along with mandatory  
16 education and participation for prescribers,  
17 pharmacists, and patients. In addition,  
18 participating prescribers and pharmacists must pass  
19 a certification test.

20 The TIRF products represent a small subset  
21 of total opioid prescriptions orders of magnitude  
22 lower than most of other products. As would be

1 expected for the low number and extensive REMS  
2 program, TIRF products are a very small part of the  
3 opioid crisis. In contrast, illicitly manufactured  
4 fentanyl is a major contributor to the opioid  
5 crisis and accounts for the majority of fentanyl  
6 related events of abuse, overdose, and death.

7 I would now like to invite Kyle Irwin to  
8 provide an overview of the TIRF REMS Access  
9 Program. Thank you.

10 **Industry Presentation - Kyle Irwin**

11 MR. IRWIN: Thank you. Dr. Pergolizzi.

12 Hello. I'm Kyle Irwin, a TIRF industry  
13 group representative from Teva Pharmaceuticals.  
14 I've worked on REMS programs for the last 10 years.  
15 The TIRF REMS Access Program is designed to ensure  
16 informed risk-benefit decisions and their  
17 appropriate use of TIRF medicines. The program  
18 requires distributors, pharmacies, prescribers, and  
19 patients to enroll. This approach restricts  
20 distribution and enables the program to achieve its  
21 goals.

22 The goals of the TIRF REMS Access Program

1 are to mitigate the risk of misuse, abuse,  
2 addiction, overdose, and serious complications due  
3 to medication errors by prescribing and dispensing  
4 TIRF medicines only to appropriate patients, which  
5 includes use only in opioid-tolerant patients;  
6 preventing inappropriate conversions between TIRF  
7 medicines; preventing accidental exposure to  
8 children and others to whom it was not prescribed;  
9 and educating prescribers, pharmacists, and  
10 patients on the potential risk of medicines.

11 The REMS includes multiple elements designed  
12 to meet the goals of the program. The first is a  
13 medication guide, which is provided with each  
14 outpatient prescription to educate the patient on  
15 the safe use of their TIRF medicine.

16 The REMS includes three elements to assure  
17 safe use: prescriber certification, pharmacy  
18 certification, and documentation of safe-use  
19 conditions for patients. These elements to assure  
20 safe use requirements are documented in the  
21 implementation system or the REMS program database  
22 and are reported to the FDA in the annual

1 assessments.

2 Because of the risks, TIRF medicines are  
3 only available through a restricted distribution  
4 system that requires educating and enrolling those  
5 who come in contact with TIRF medicines. The TIRF  
6 REMS Access Program is mandatory for distributors,  
7 pharmacies, prescribers, and patients.  
8 Manufacturers of TIRF medicines only ship to  
9 distributors enrolled in the REMS. Enrolled  
10 distributors only ship TIRF medicines to pharmacies  
11 enrolled in the REMS.

12 Pharmacies are required to verify the  
13 prescribers enrolled in the REMS before dispensing  
14 any TIRF medication. The program continually  
15 monitors participants using a noncompliance  
16 protocol and annual assessments review the  
17 program's effectiveness.

18 To prescribe a TIRF medicine, a healthcare  
19 provider is required to enroll in the TIRF REMS  
20 Access Program. In order to enroll, the prescriber  
21 must review the education program, successfully  
22 complete the knowledge assessment with a score of

1 100 percent, and complete and submit the prescriber  
2 enrollment form to the program. This whole process  
3 typically takes about 30 minutes. The education  
4 materials and enrollment form advise the prescriber  
5 to review the prescribing information for specific  
6 TIRF products. The prescriber must also re-enroll  
7 every two years.

8 For each appropriate patient, the prescriber  
9 must provide a copy of the medication guide,  
10 counsel the patient about the risks, benefits, and  
11 proper use of their TIRF medicine, and complete,  
12 sign with the patient, and submit a  
13 patient-prescriber agreement form, or PPAF, to the  
14 program.

15 On the PPAF, both prescribers and their  
16 patients acknowledge the key risk messages and  
17 program requirements. This interaction is  
18 consistent with best practices for prescribing  
19 opioids and not unduly burdensome.

20 The PPAF must be submitted by the prescriber  
21 to the REMS program within 10 business days of the  
22 first authorized fill. The PPAF can be submitted

1 real time via the TIRF REMS Access Program website  
2 or faxed to the contact center.

3 Patients are passively enrolled in the TIRF  
4 REMS Access Program at the point of their first  
5 outpatient prescription fill. The signed PPAF  
6 serves as their official enrollment form for the  
7 patient and must be received within 10 business  
8 days of the patient's first dispense.

9 A patient and caregivers overview and  
10 medication guides are available to educate the  
11 patient. These materials help the patient  
12 understand the safe use, appropriate storage, and  
13 risks of the TIRF products. If the patient has a  
14 gap of 6 months or more until their next fill, a  
15 new PPAF must be signed and submitted.

16 PPAFs must be renewed every two years. A  
17 patient can call the contact center with questions  
18 or visit the program website to find educational  
19 materials. Patients receiving TIRF medicines in an  
20 inpatient setting such as hospitals, hospices, and  
21 long-term care facilities are not required to  
22 enroll in the program.

1           In inpatient and outpatient pharmacies,  
2       including closed pharmacy systems, dispensing TIRF  
3       medicines must be enrolled in the REMS. In order  
4       for a pharmacy to enroll, a designated pharmacy  
5       authorized pharmacist must review the education  
6       program, successfully complete a knowledge  
7       assessment with a score of 100 percent, and  
8       complete and submit the pharmacy enrollment form to  
9       the program. The authorized pharmacist is  
10      responsible for training other pharmacy staff with  
11      the risks associated with TIRF medicines and the  
12      requirements of the REMS.

13           Prior to dispensing a TIRF medicine, the  
14      pharmacy must receive an REMS authorization, which  
15      verifies that the requirements have been met. A  
16      majority of pharmacies receive this authorization  
17      through the same transaction used for payment  
18      adjudication in the pharmacy network. This  
19      real-time automated process for validating REMS  
20      requirements is incorporated into the pharmacy  
21      standard workflow. It reduces burden on the  
22      pharmacy staff and facilitates compliance with the

1 program.

2 The REMS authorization checks for three  
3 criteria: is the pharmacy enrolled; is the  
4 prescriber enrolled; and has a PPAF been signed and  
5 submitted to the program or is it within the  
6 10-business-day window of a first prescription? If  
7 the REMS requirements are not met, the pharmacy is  
8 advised they must not dispense the drug, and the  
9 claim does not process any further.

10 If requirements are met, the prescription is  
11 REMS authorized, and the TIRF medicine is eligible  
12 to be dispensed. Closed-system pharmacies outside  
13 of the pharmacy network must manually obtain the  
14 authorization from the REMS program via phone or  
15 fax.

16 The REMS pharmacy network is also known as  
17 the switch. It connects to the pharmacy with  
18 third-party insurers. The REMS authorization check  
19 occurs before the transaction is submitted to the  
20 third-party insurer. This transaction takes place  
21 within milliseconds. Pharmacies enrolled in the  
22 REMS attest that all TIRF prescriptions, regardless



1 of method of payment, must be processed via the  
2 pharmacy network. This authorization includes  
3 processing cash payments through the network for  
4 REMS authorization.

5 To become enrolled, a distributor must also  
6 complete a distributor enrollment form. Prior to  
7 shipping any TIRF medicines, the distributor is  
8 required to verify pharmacy enrollment in the REMS.  
9 They must agree to train relevant staff on REMS  
10 requirements and comply with periodic audits in  
11 noncompliance investigations. Distributors must  
12 re-enroll in the REMS every two years.

13 In conclusion, the restricted distribution  
14 system prevents prescribing and dispensing outside  
15 of the TIRF REMS Access Program. Mandatory  
16 education, knowledge assessments, enrollment of  
17 pharmacies and prescribers provides a baseline  
18 understanding of the risks and appropriate use of  
19 TIRF medicines. Medication guides, the PPAF, and  
20 other educational materials facilitate risk-benefit  
21 discussions between prescribers and their patients  
22 or caregivers. And finally, the use of the

1 Pharmacy Network for the REMS authorization reduces  
2 burden on the pharmacies.

3 Now, Dr. Annette Stemhagen will discuss the  
4 assessment results.

5 **Industry Presentation - Annette Stemhagen**

6 DR. STEMHAGEN: Thank you, Kyle.

7 I'm Annette Stemhagen, an epidemiologist and  
8 senior vice president and chief science officer at  
9 UBC. I've been working in the field of risk  
10 management since 2000. UBC conducts analyses as  
11 part of the REMS evaluation and prepares the REMS  
12 assessment reports. There is ongoing evaluation of  
13 the TIRF REMS Access Program. The TRIG and the FDA  
14 use the annual assessments to determine the  
15 effectiveness of the REMS in meeting its goals.

16 The most recent assessment covers the sixth  
17 year of the program and also includes cumulative  
18 data from REMS launched through October 2017. The  
19 current REMS assessment includes data on program  
20 utilization such as enrollment data, dispensing  
21 data, and noncompliance data, which show that  
22 patients and prescriptions are declining and

1 overall compliance has been good.

2 The FDA requested two studies to further  
3 assess the REMS, which will be discussed later.  
4 These studies assess prescribing of TIRFs to opioid  
5 non-tolerant patients and to evaluate persistency  
6 or switching from one TIRF medicine to another.  
7 The assessment report also includes safety  
8 surveillance data using spontaneously reported  
9 adverse events of special interest that is  
10 collected by all TIRF REMS sponsors and aggregated  
11 to identify trends.

12 Annual knowledge, attitude, and behavior, or  
13 KAB surveys, which measure prescriber, pharmacist,  
14 and patient knowledge and behaviors related to the  
15 TIRF medicines, show high overall rate of  
16 understanding and have identified one concept that  
17 has lower comprehension.

18 Dr. Dart will show in the research abuse  
19 diversion and addiction related surveillance, or  
20 RADARS system, that TIRF products represent a very  
21 small proportion of opioid events. Metrics of  
22 program utilization over the past three years, show

1 a decline in participation in the REMS program.

2 The number of prescriptions authorized,  
3 shown in green and on the right Y-axis during each  
4 reporting period, have declined from October 2013  
5 to October 2017, a total of 65 percent. During the  
6 same period, the number of active patients  
7 participating in the program, shown in blue and on  
8 the left Y-axis, declined at a similar rate. The  
9 declining prescribers, shown in purple on the left  
10 Y-axis was not as steep.

11 Although we don't know all the reasons for  
12 these declines, the data show that declines are  
13 primarily due to enrollment expiration without  
14 re-enrollment. Prescribers must re-enroll every  
15 two years. Active outreach is done to remind  
16 prescribers and pharmacists of the requirement to  
17 re-enroll in order to continue to prescribe or  
18 dispense.

19 Additional outreach was conducted to  
20 determine reasons why stakeholders are not  
21 enrolling. The main responses were that the  
22 pharmacy had no patients that required a TIRF

1 prescription, and prescribers have changed their  
2 prescribing.

3 As of October 2017, a total of over 745,000  
4 prescriptions have been submitted to the TIRF REMS  
5 Access Program for from outpatient pharmacies. Of  
6 these, 89.2 percent did not encounter any REMS  
7 related rejection prior to being authorized,  
8 showing that the vast majority of prescriptions  
9 were appropriate and met REMS requirements.

10 Of the remaining 11 percent, 3.1 percent  
11 were eventually authorized since the reasons for  
12 rejection were primarily related to PPAF issues  
13 that were readily corrected. The remaining  
14 7.7 percent largely arose from prescriptions  
15 submitted by prescribers not in the program and  
16 were appropriately rejected.

17 Stakeholder noncompliance with the REMS  
18 requirements is identified in several ways and  
19 investigated as per a noncompliance protocol.  
20 Noncompliance is measured by operational metrics  
21 such as timely submission of PPAFs or prescriptions  
22 dispensed without authorization and reports to the

1 call center, or from vendors, or sponsors.

2 Additional noncompliance may be found  
3 through inpatient pharmacy audits and closed-system  
4 pharmacy dispensing reconciliation with the REMS.  
5 Noncompliance results in an escalated process, from  
6 a notice, to a warning letter, to suspension, to  
7 ultimately deactivation.

8 The REMS works with the prescriber to  
9 address issues of noncompliance and prevent future  
10 cases. In instances of severe noncompliance or in  
11 the event that the prescriber refuses to work with  
12 the program, they are deactivated.

13 The events of noncompliance have been  
14 declining over the time period in which the REMS  
15 has been active. Since the beginning of the  
16 program, there have been 471 confirmed instances of  
17 stakeholder noncompliance. The majority, 377,  
18 involved prescribers; 91 involved pharmacists; and  
19 3 involved distributors.

20 The majority of prescriber noncompliance was  
21 as a result of not having a completed PPAF on file  
22 within the required 10 days after the patient's

1 first REMS medicine dispensed. The most common  
2 reason for a non-closed system pharmacy's  
3 noncompliance is dispensing a prescription without  
4 REMS authorization.

5 The majority of noncompliance is resolved  
6 through interaction with the stakeholder. However,  
7 over the course of the program, 11 prescribers have  
8 been deactivated for noncompliance. No pharmacies  
9 have been deactivated for noncompliance.

10 Random samples of inpatient and  
11 closed-system pharmacies are audited regularly.  
12 Yearly audits of inpatient pharmacies include  
13 review of staff training and verification that  
14 order sets and processes are in place to comply  
15 with the REMS requirements. Annual audits of  
16 closed-system pharmacies reconcile prescriptions  
17 received and dispensed with REMS authorizations.

18 In the most recent assessment, there were no  
19 adverse audit findings among the 5 inpatient  
20 pharmacies that were audited. Eighteen percent of  
21 the prescriptions evaluated in closed-system  
22 pharmacies were found to have been dispensed

1 without obtaining a REMS authorization. As per the  
2 noncompliance protocol, warning letters and  
3 educational outreach were performed to each  
4 noncompliance site.

5           There are a number of additional controls  
6 built into the REMS to ensure compliance such as  
7 those around PPAFs. The program does not allow a  
8 patient to have more than 3 prescriptions in the  
9 first 10 working days after initiating a TIRF  
10 medicine without a PPAF. This is to allow for  
11 titration. Likewise, there should be no  
12 prescription dispensed after 10 working days if a  
13 PPAF has not been received. Neither of these  
14 scenarios has occurred in the last two years of the  
15 program.

16           At the request of FDA, the TRIG conducted  
17 two studies as part of the evaluation of the  
18 success of the REMS. The first examined compliance  
19 with the requirement that all patients be opioid  
20 tolerant before initiating a TIRF product. The  
21 second evaluated the number of patients who  
22 switched from one TIRF product to another.



1           There's no direct way to assess whether a  
2       patient is opioid tolerant using REMS data. The  
3       REMS database does not collect any information on  
4       any other medications other than TIRF medicines.  
5       Other databases are also difficult to use to  
6       evaluate compliance with opioid tolerant since TIRF  
7       medicines are taken on an as-needed basis.

8           For example, there may be data showing that  
9       the TIRF and the around-the-clock opioid were first  
10      dispensed at the same time, but it's possible that  
11      the TIRF product may not have been used for a  
12      period of several weeks after the initiation of the  
13      around-the-clock opioid; or the patient could have  
14      started on the around-the-clock opioid as an  
15      inpatient.

16          Despite these limitations, a study used the  
17      IQVIA longitudinal database to assess prescribing  
18      patterns, looking for the timing of a first TIRF  
19      medication dispensed relative to prior dispensing  
20      of the around-the-clock opioid. The opioid  
21      tolerance study was a retrospective cohort study  
22      conducted using data from the IQVIA longitudinal

1 prescriptions database for the period of February  
2 2012 to October 2015.

3 At the time of the study, the LRx database  
4 contained electronic dispensing records  
5 representing prescriptions for 86 percent of the  
6 outpatient retail pharmacy channel. Inpatient  
7 analgesic use is not captured, potentially causing  
8 an underestimation of opioid tolerance for recently  
9 hospitalized patients.

10 The definition of opioid tolerance used in  
11 this study as per product labeling has two  
12 dimensions. The first is that patients must be on  
13 an around-the-clock opioid for one week or longer  
14 immediately proceeding the TIRF. Second, the dose  
15 must be stated in each product label and as  
16 described in this slide.

17 In this study, a total of 21,286 patients  
18 were dispensed an initial prescription for a TIRF  
19 product in the outpatient setting. Patients had to  
20 have at least one prescription claim for any  
21 marketed product prior to their TIRF to prevent  
22 patients being classified as having no opioid

1 history due to lack of data capture rather than a  
2 true lack of a prescription.

3 Eighty-six percent of unique patients  
4 received an outpatient opioid analgesic  
5 prescription in the 30 days prior to the TIRF  
6 prescription. Using the definition of opioid  
7 tolerant consistent with the TIRF labels,  
8 approximately 42 percent of patients who received  
9 initial outpatient TIRF product filled were  
10 considered opioid non-tolerant. However, again,  
11 misclassification may occur since TIRFs are used as  
12 needed.

13 A one-time persistency analysis was  
14 conducted at FDA's request to determine how many  
15 TIRF patients are switching from one TIRF regimen  
16 to another. This is considered the population  
17 potentially at risk of an inappropriate conversion.  
18 While this analysis used data on all TIRF  
19 prescriptions authorized in the REMS, there are  
20 several limitations. The analysis included the  
21 first TIRF REMS prescription after the REMS began,  
22 and the patient could have had a prescription of a

1 TIRF in an earlier time period. The REMS only  
2 includes outpatient TIRF, so any TIRF used while  
3 the patient may have been hospitalized was not  
4 included.

5 Patients who had at least 2 TIRF  
6 prescriptions between March 12, 2012 and October  
7 28, 2015 were included in the analysis. A total of  
8 18,160 patients were included. Persistency was  
9 presented as a percentage of patients who displayed  
10 continuous use of the TIRF regimen for the entire  
11 duration of the observation period.

12 Eighty-one percent of patients remained on  
13 their index TIRF regimen during the observation  
14 period. Nineteen percent of patients made at least  
15 one regimen switch from their index TIRF medicine.  
16 However, dosing data were not used in this  
17 persistency analysis, so there was no way to  
18 identify whether any of the conversions were  
19 inappropriate.

20 The TRIG performs continuous safety  
21 surveillance by monitoring adverse events of  
22 special interest received by the individual

1 sponsors. These are addiction, overdose, death,  
2 and pediatric exposures. Each manufacturer  
3 identifies relevant reports within their safety  
4 database using a standard protocol, which uses both  
5 MedDRA codes text-string searches. UBC aggregates  
6 the data, which are then reviewed by an independent  
7 healthcare professional.

8 In order to avoid duplication of cases  
9 between sources and among sponsors, the analysis  
10 excludes literature reports and reports from poison  
11 centers. There are well-known limitations of  
12 spontaneous reports as outlined in both the FDA and  
13 the TRIG meeting information materials, and is  
14 highlighted here.

15 In the most recent reporting period, there  
16 were 568 reports of adverse events of special  
17 interest. The majority were deaths, many with no  
18 cause indicated. Smaller numbers of reports were  
19 classified as addiction and overdose. The number  
20 of deaths reported to the TRIG showed an increase  
21 in the most recent time period compared to the  
22 previous two time periods. This may partly be an

1 effective REMS outreach and processes instituted  
2 investigating non-renewals of PPAFs, which may have  
3 identified non-PPAF renewal due to patient death.

4 Since October 2013, there were 549 deaths  
5 reported to the TRIG. Of these, 355 had  
6 insufficient information to allow for an assessment  
7 of causality. 187 deaths were determined to be not  
8 related to a TIRF medicine. There were only 7  
9 reports that by the reporter were considered  
10 related or possibly related to a TIRF medicine.  
11 261 of the 549 reports of deaths were related to  
12 breakthrough pain, breakthrough cancer pain, and/or  
13 a cancer diagnosis. But again, if you're familiar  
14 with spontaneous reports, there's a lot of missing  
15 data in these reports.

16 Reports of addiction have been low and  
17 variable over time. In the most recent reporting  
18 period, there were 10 reports of addiction, one of  
19 which resulted in death. However, there was  
20 insufficient outcome information provided for the  
21 remaining cases. The number of overdose cases was  
22 low but showed an increase in the most recent

1 reporting period; 24 had an outcome of death.

2 One factor that may be contributing to the  
3 increases could be stimulated reporting from the  
4 increased media coverage of the opioid epidemic.  
5 For example, 21 of those 24 reports of overdose  
6 resulting in death were from one reporter in what  
7 appeared to be information coming from a newspaper  
8 article.

9 There were 17 reports of childhood exposure  
10 and an adverse event analysis, which began with the  
11 36-month reporting period. All reports of  
12 pediatric exposure were a result of intentional  
13 prescribing. Fourteen cases had no events but were  
14 reported based solely on patient age. One report  
15 included an outcome, which was death. The reporter  
16 and attorney declined to provide any details.

17 The REMS seek to educate all stakeholders  
18 about the risks of TIRF products and the REMS  
19 requirements. Attained education is first measured  
20 with the knowledge assessments that are part of the  
21 enrollment process for prescribers and pharmacies  
22 and for which they must attain a 100 percent score.

1 During the REMS operational phase, knowledge,  
2 attitudes and behavior surveys are conducted  
3 annually with each stakeholder group.

4 Annual KAB surveys measure understanding of  
5 appropriate use of TIRF medicines and the REMS  
6 requirements. The surveys were developed to  
7 measure the key risk messages of the REMS. Each  
8 key risk message includes multiple questions or  
9 items that are scored separately. When developing  
10 the survey, qualitative testing was done to ensure  
11 that questions and response options were clear and  
12 understandable by all stakeholders.

13 Based on FDA feedback, the goal to  
14 demonstrate understanding is a correct response  
15 rate of 80 percent or greater. The survey invites  
16 all eligible prescribers and patient stakeholders  
17 in the REMS database to participate; it is not a  
18 sample. All closed-system and inpatient pharmacies  
19 are also invited. The only sample is a random  
20 sample of non-closed-system pharmacies because the  
21 number of those pharmacies enrolled in the REMS is  
22 very large. The survey protocol includes due



1 diligence of at least three outreach attempts to  
2 invitees to maximize the response rate.

3 In general, patient and caregiver knowledge  
4 has remained stable over time. The 72-month survey  
5 shows a high level of patient understanding of key  
6 risk messages with an average knowledge score for 5  
7 of the 6 key risk messages greater than 86 percent.  
8 Patients scored consistently low on the following  
9 items within one key risk message. TIRF medicines  
10 should not be taken for pain after surgery, for  
11 long lasting pain not from cancer, or for headache  
12 pain. A patient must stop taking their TIRF  
13 medicine if they stop taking their around-the-clock  
14 medicine.

15 Results from the most recent prescriber and  
16 pharmacist KAB surveys show that the overall  
17 knowledge scores for prescribers were 89.6 percent  
18 with average knowledge scores greater than  
19 87 percent for each of the 4 key risk messages.  
20 Similarly, the overall knowledge score for  
21 pharmacists was 84.9 percent with average knowledge  
22 scores of at least 85 percent for each of the key

1 messages.

2 Prescribers had high scores for most  
3 questions about defining opioid tolerance and  
4 selecting the right patients who are opioid  
5 tolerant. Scores have been consistently high over  
6 the waves of the survey. There were, however,  
7 3 messages that had scores less than 80 percent  
8 over time.

9 The first, understanding that a patient may  
10 not start a TIRF medicine and an around-the-clock  
11 opioid on the same day. A patient must stop taking  
12 their TIRF if they stop taking an around-the-clock  
13 medicine, and TIRF medicines are not indicated for  
14 chronic non-cancer pain.

15 When patient, prescriber, and pharmacy  
16 survey respondents were compared to the appropriate  
17 IQVIA data set, or REMS data for pharmacies, there  
18 were some similarities and some differences.  
19 However, in all instances, when the survey results  
20 were adjusted to the general population  
21 characteristics, the knowledge scores were similar.

22 There are a number of ways that the REMS is

1 continually evaluated for effectiveness.

2 Operational metrics concerning the REMS program  
3 showed that the number of active patients and the  
4 number of TIRF prescriptions have been declining  
5 over the past three years. This is likely due to  
6 changes in the prescribing environment.

7 Compliance monitoring in the REMS shows that  
8 stakeholders are following the REMS requirements  
9 with few deactivations due to noncompliance. Since  
10 some of the REMS evaluations using existing data  
11 have limitations, additional studies are planned or  
12 underway using external data sources, and they will  
13 be presented later in this talk.

14 I'm now going to turn the program over to  
15 Dr. Dart.

16 **Industry Presentation - Richard Dart**

17 DR. DART: Good morning. I'm Rick Dart.  
18 I'm the executive director of the RADARS system.  
19 We perform surveillance of prescription opioids  
20 such as those in the TIRF REMS. The RADARS system  
21 is operated by the Denver Health and Hospital  
22 Authority, which is the public hospital for the

1 city and county of Denver, Colorado.

2 RADARS is an independent nonprofit  
3 organization that is supported by about 20  
4 different pharmaceutical companies and government  
5 agencies. By contract, companies can only use this  
6 data for risk management functions. None of these  
7 entities participate in developing the system and  
8 data collection or an analysis of the data. None  
9 have access to the raw data.

10 How does one measure abuse and addiction  
11 that a person is unlikely to admit? We do it by  
12 collecting data when a person is forced to reveal  
13 themselves. We like to call this mosaic  
14 surveillance. By combining the results of  
15 different programs, we can create a more complete  
16 understanding of how often and why a drug is  
17 abused.

18 For example, poison centers receive a very  
19 large number of calls involving substance abuse.  
20 These calls typically involve a person or their  
21 friend calling when something occurs that worries  
22 them about the drugs they took.

1           Another time that abuse and addiction become  
2     apparent is when a person enters treatment for  
3     substance abuse. In our opioid treatment program  
4     and the survey of key informant patients, we  
5     confidentially and anonymously survey patients as  
6     they enter treatment for substance abuse. Finally,  
7     we also perform a Web-based survey called the  
8     Survey of Non-Medical Use of Prescription Drugs,  
9     and this tool gives us a much wider view and allows  
10    us to identify specific groups like college  
11    students.

12           One of the strengths of the RADARS system is  
13    that we collect product-specific data. Each  
14    program goes to great lengths to not only identify  
15    the active pharmaceutical ingredient like fentanyl,  
16    but to determine the specific product and  
17    formulation that was used. For example, we  
18    distinguish an extended-release product like the  
19    Duragesic patch from immediate-release products  
20    like Fentora. Fortunately, the physical  
21    characteristics of the transmucosal products  
22    actually improves our ability to identify the

1 product.

2 Now, I'm going to examine the results of our  
3 mosaic surveillance starting with health events in  
4 the poison center system. Just as a reminder, a  
5 poison center receives calls from people who are  
6 concerned about a drug or chemical that they have  
7 been exposed to, and the poison centers that  
8 participate in the RADARS system cover over 94  
9 percent of the population and include all ages.  
10 Each case is classified when it comes into a poison  
11 center based on the assessment of a trained nurse  
12 or pharmacist.

13 For opioid analyses, we typically look at a  
14 category called intentional abuse, which is defined  
15 on the slide. And essentially, it boils down to a  
16 person took the drug to get high.

17 We think that RADARS' poison center data are  
18 appropriate for assessing fentanyl products. The  
19 Drug Abuse Warning Network, also known as DAWN, was  
20 a program run by SAMHSA that collected drug abuse  
21 data from a nationally representative sample of  
22 emergency departments throughout the U.S. We

1 routinely compared our poison center data with DAWN  
2 until it was discontinued in 2011, but we had this  
3 data. And as you can see, fentanyl, and really all  
4 the other analgesics in RADARS poison centers,  
5 correlate well with DAWN.

6 Despite the extensive coverage by poison  
7 centers, the absolute number of cases reported to  
8 poison centers for TIRF products is low. The  
9 vertical axis here shows the number of cases, not a  
10 rate, per calendar quarter for the entire study  
11 period, and there were a total of just 24  
12 intentional abuse cases received by poison centers  
13 during the surveillance period. The highest  
14 quarter was the second quarter of 2014 with 3  
15 cases, and there was an average of just 3.4 cases  
16 per year. For comparison, oxycodone immediate  
17 release has over 5,000 cases per year  
18 [indiscernible]

19 A big challenge with low case numbers is  
20 misidentification. For example, if a few cases of  
21 oxycodone immediate release are misidentified, the  
22 error constitutes a tiny portion of the total

1        number of oxycodone cases. However, in the case of  
2        TIRF products, just a couple of misidentifications  
3        can alter the rates substantially as you can see;  
4        and indeed, the FDA will be addressing this  
5        phenomenon later, especially in relation to the  
6        treatment centers, which I'll talk about in a few  
7        minutes.

8                Now, if I take those 24 cases and divide by  
9        the population of the same area, the TIRF product  
10       rate is shown here and is much lower than the  
11       overall rates for comparator opioids. For most of  
12       my remaining slides, I'll be showing the mean and  
13       95 percent confidence intervals of the pre-REMS and  
14       post-REMS data, as shown here. The surveillance  
15       protocol specified for comparator opioids:  
16       immediate-release oxycodone, extended-release  
17       oxycodone, immediate-release hydromorphone, and  
18       immediate-release oxymorphone.

19               I've chosen hydromorphone to show our most  
20       slides because it's also a very potent, highly  
21       desired product as well, and it had the least  
22       confounding of the comparator drugs, but please



1       note that there were 879 hydromorphone cases  
2       reported during the study period compared to the 24  
3       for TIRF. The results for the other comparator  
4       drugs are similar, and I have those data on backup  
5       slides if the committee would like to see them.

6               We know that the number prescriptions  
7       dispensed for the transmucosal products is lower  
8       than the other opioid classes, and this slide shows  
9       the data from the previous slide. But instead of  
10       dividing by population, we've now divided by the  
11       number of prescriptions dispensed for the TIRF  
12       products combined.

13               For the TIRF products, the average rate is  
14       about 0.5 cases per 10,000 prescriptions. This is  
15       similar to immediate-release hydromorphone. You  
16       can see that the TIRF rate has increased some in  
17       the last couple of years. We're not sure of the  
18       reason for this increase or, frankly, even that  
19       it's real given the very low number of cases. For  
20       example, in the first quarter of 2017, which is the  
21       highest rate on this figure, the red circle, that  
22       was a total of 2 cases.

1           Mathematically, the increased rate is due to  
2           a decreasing denominator. We can see that effect  
3           by displaying the prescriptions dispensed onto the  
4           raw number of cases shown here. The number of  
5           cases has remained essentially the same, but the  
6           number of prescriptions dispensed has decreased  
7           greatly.

8           So why are those numbers maintained? Well,  
9           there are at least three plausible reasons. First,  
10          the data may simply be accurate. With small  
11          numbers, it's certainly possible that one or two  
12          cases of accurately identified TIRF abuse were  
13          called to a poison center each quarter. A small  
14          number of committed abusers who have access to the  
15          drug can account for such a small number of cases  
16          even as total exposure to the drug falls.

17          Second, it's important to remember,  
18          especially for drugs with low prescription volumes,  
19          that not all prescription products abused arise  
20          from a legitimate prescription. For example,  
21          products can be stolen, and they won't be  
22          represented as a new prescription in the data. We

1 have also published on products coming to the U.S.  
2 from other countries, so these could be  
3 pharmaceutical products from another country. And  
4 the third reason is misidentification. It's  
5 possible that a caller told the poison center what  
6 they thought they had abused, but it may have been  
7 another drug that they actually abused.

8 This is another poison center category,  
9 which is called unintentional general exposure, and  
10 this is where all the pediatric cases fall, and it  
11 shows the same pattern. The definition of  
12 unintentional general in poison centers is all  
13 unintended exposures that are not specifically  
14 defined elsewhere in our coding book

15 There were a total of 18 pediatric cases  
16 resulting in very low rates. None of the cases  
17 died. The rates for hydromorphone and comparators  
18 were higher. When we adjust for prescriptions  
19 dispensed again, the mean rate rises for the TIRF  
20 drugs to roughly the same as the comparator group  
21 and does not appear to be increasing.

22 Poison centers stay with a case until it's

1 resolved; therefore, we can record the outcome of  
2 each case. We classify those as mild, moderate,  
3 major, or death. Here, I've looked at the more  
4 severe cases by combining the categories of major  
5 outcome or death over the study period. That rate  
6 of major outcome and death for the TIRF products is  
7 lower than the comparators when adjusted for  
8 population.

9 Please be aware that 19 of these cases were  
10 in the major category. There have been just two  
11 deaths with TIRF products that were poison center  
12 cases, and those both occurred in 2013.

13 Here are those same data again, as we saw in  
14 the previous slide, but now adjusted for those  
15 prescriptions dispensed as I did before.

16 Currently, poison centers receive about one case  
17 involving a TIRF and resulting in a major outcome  
18 or death for every 20,000 prescriptions dispensed.  
19 Again, we see that the falling number of  
20 prescriptions for the TIRF products has resulted in  
21 an increase in the prescription rate over time; but  
22 again, that highest rate had a total of 2 cases.

1           There are several other categories in poison  
2       centers. This figure shows the results for all of  
3       those case categories in the TIRF surveillance  
4       program using the population denominator. The  
5       boxes in yellow are the categories I've already  
6       shown you.

7           For example, the intentional abuse data I've  
8       shown you are on the far left. Next is the  
9       category of ED visits or hospitalization, then  
10      major outcome or death; intentional misuse;  
11      unintentional general, which I showed you;  
12      pediatric unintentional, which means patients less  
13      than 6 years; and finally, therapeutic error.

14          The TIRF products are the lowest in each  
15      category. But again, when we can take the same  
16      data and express it per 10,000 prescriptions  
17      dispensed, the TIRF drugs, the black column on the  
18      left of each box, are no longer the lowest.  
19      Instead, they seem to be about in the middle of the  
20      pack. As I mentioned earlier, even a few committed  
21      abusers can create a measurable rate when the  
22      number of prescriptions is low.

1           Now, another important perspective is that  
2       of persons entering treatment for substance abuse.  
3       RADARS has two programs that collect cases from  
4       people entering treatment. And in both programs,  
5       the person entering treatment completes a survey  
6       indicating what drugs they have abused in the past  
7       30 days to get high.

8           We typically combine the data from these two  
9       programs, especially in the cases with low rates of  
10      abuse, such as we have with the TIRF products.  
11      Overall, there are about 200 programs across nearly  
12      all states that provide data.

13          As we've described, fentanyl is a very  
14      desirable opioid. Thus, we generally anticipate  
15      fairly high rates for the fentanyl products and  
16      treatment programs. When we look at the treatment  
17      center rates adjusted for population, we can see  
18      that, once again, the TIRF products are low and  
19      approach zero in 2017. In contrast,  
20      immediate-release hydromorphone is much higher.

21          Again, we do that adjustment where we divide  
22      now by prescriptions instead of population, and we

1       see the same effect that we saw in the poison  
2       center data. The TIRF rate rises and is now higher  
3       than the immediate-release hydromorphone. Again,  
4       this calculation is driven by the falling number of  
5       prescriptions, not from an increasing number of  
6       cases. In 2010, there were about 90 TIRF cases  
7       reported per calendar quarter. In contrast, these  
8       have decreased to about 30 per quarter in 2017.

9               Here we see the other comparators in the  
10       treatment programs all at once. The TIRF group of  
11       products, the column in black on the left, is much  
12       lower than the comparators when viewed from the  
13       perspective of number of events divided by  
14       population. And again, after adjustment for  
15       prescriptions, we see that the cases per 10,000  
16       prescriptions is higher than 3 of the comparators  
17       and lower than oxymorphone.

18              Moving to the next program, the survey of  
19       non-medical use of prescription drugs, or NMURx, is  
20       a Web-based survey of the general adult population.  
21       The survey is offered to a very large group of  
22       participants. We get 30,000 respondents per survey

1 twice a year in the United States. The survey uses  
2 a specific definition of non-medical use, use  
3 without a doctor's prescription or for any reason  
4 other than what was recommended by your doctor. So  
5 this definition includes both abuse and misuse.

6 The survey was added to the TIRF  
7 surveillance program specifically to examine  
8 non-medical use by college students because we have  
9 that category in the study. And the green columns  
10 here represent non-medical use in the last year,  
11 and the light green columns represent non-medical  
12 use in the last 30 days. As you can see, the TIRF  
13 products as a group are generally lower than  
14 oxycodone and similar to hydromorphone and  
15 oxymorphone.

16 Overall, my assessment is that the potential  
17 for abuse of a TIRF group of drugs is high, but the  
18 REMS and likely other factors have actually  
19 decreased the misuse and abuse of these products.  
20 It seems likely that without the TIRF REMS, rates  
21 would be higher in this concrete, and this  
22 conclusion is supported by similar findings



1 throughout the different programs.

2 The 50 poison centers in RADARS received  
3 just a total of 3 to 4 abuse cases involving a TIRF  
4 product annually, which is strikingly low. When we  
5 adjust for utilization, meaning divided by that  
6 number of prescriptions dispensed, some categories  
7 of poison center rates are higher for the TIRF  
8 products and others are lower. Poison center cases  
9 ending in death are very rare.

10 There were just 2 cases in 2013 and none,  
11 fortunately, in the last 4 years of the  
12 surveillance. But because poison center cases do  
13 not all involve all cases, it's a spontaneous  
14 reporting system, it's the trend here that's  
15 important rather than the absolute numbers. In  
16 treatment centers, it's clear that the TIRF  
17 products are used to some degree, but their abuse  
18 is low and not increasing. And for college  
19 students, there does seem to be some abuse of the  
20 TIRF products, but it's generally lower than the  
21 comparator drugs.

22 I'll now turn this over to Dr. Mariano,

1 who's going to talk about the effectiveness of the  
2 TIRF REMS access program.

3 **Industry Presentation - Dean Mariano**

4 DR. MARIANO: Good morning. I'm Dean  
5 Mariano. I'm an anesthesiologist with additional  
6 board certifications in pain management and  
7 addiction medicine. I'm TIRF REMS certified and  
8 have been for six years. I'm the immediate past  
9 president of the Connecticut Pain Society and the  
10 former chairman of the Connecticut State Medical  
11 Society's task force on opioids. Last year, I  
12 joined Insys as senior director of clinical  
13 development and head of medical affairs. I now  
14 come to the TIRF REMS Access Program from two  
15 perspectives, that of a clinician and that of  
16 industry.

17 The TIRF REMS Access Program has  
18 demonstrated effectiveness since its inception and  
19 has continued to evolve to adjust the changing  
20 prescribing environment. The TIRF REMS Access  
21 Program is part of an array of other regulations  
22 and guidances that govern prescribing of all opioid

1 medications.

2 Prescribers of any opioid pain medication  
3 need to properly assess all patients prior to  
4 prescribing and follow safe prescribing practices  
5 that include assessments of the risk of abuse,  
6 addiction, and diversion for each individual  
7 patient. Periodically, prescribers must reevaluate  
8 both therapy for effectiveness and for risk  
9 management. They must keep detailed records of all  
10 prescribing information.

11 Lastly, they must monitor for compliance.  
12 This monitoring can take several different forms,  
13 including urine drug testing to ascertain  
14 compliance, pill counts, and participation in  
15 state-run prescription drug monitoring programs.  
16 The majority of states have mandated that  
17 physicians participate in these prescription  
18 monitoring programs to monitor compliance, doctor  
19 shopping, and the patient's opioid profile.

20 In addition, the entire supply chain,  
21 including manufacturers, distributors, and  
22 pharmacies, along with prescribers, must follow

1 federal law enforced by the DEA governing the use  
2 in handling of controlled substances. There are  
3 mandated practices to prevent diversion, including  
4 a closed distribution system, tracking of  
5 inventory, and processes to identify suspicious  
6 orders to authorities. Patients also have the  
7 responsibility to protect against theft and  
8 accidental exposure for all scheduled pain  
9 medications.

10 Patients are required to store their opioid  
11 pain medications in a locked storage space to which  
12 they have exclusive access. They are to keep them  
13 out of sight of anyone who may enter the home, such  
14 as children, teens, neighbors, contractors, and  
15 guests.

16 Some opiates have child safety kits that  
17 further reduce the risk of accidental exposure in  
18 the home. Plus, patients are also instructed to  
19 dispose of any unused or residual medications  
20 usually through product-specific instructions.  
21 Further, they're informed that they may never give  
22 anyone else their medications because of harm or

1 death, even if the person has the same symptoms.

2 It is against the law to sell or give away opioid  
3 pain medications.

4 The TIRF REMS Access program is part of this  
5 broad set of laws, regulations, and practices that  
6 govern opioid pain medicines. The TIRF REMS Access  
7 Program must thread the needle of its own benefits  
8 and risks. There's a delicate balance between  
9 restricting access so that only appropriate  
10 patients receive the product and unduly limiting  
11 TIRF medicines to patients who need them.

12 The program should not result in  
13 undertreatment of breakthrough cancer pain, but at  
14 the same time, it must mitigate the risks  
15 associated with that treatment, as well as the  
16 risks of exposure to inappropriate patients or  
17 accidental or intentional exposure in non-patients.

18 To do this, the program includes extensive  
19 education for all stakeholders. It minimizes risks  
20 and mitigates risks. Ultimately, by reducing the  
21 risks associated with the TIRF medicines, enabling  
22 their use to effectively manage breakthrough cancer

1 pain, as well as reducing inappropriate use of  
2 other opioids to treat breakthrough cancer pain,  
3 the access program reduces overall burden on the  
4 healthcare system.

5 Before the implementation of the TIRF REMS  
6 Access Program, the risks were not adequately  
7 managed. Prior to the TIRF REMS Access Program,  
8 medication errors accounted for more than  
9 two-thirds of all adverse events reported to the  
10 agency.

11 There were also serious adverse events,  
12 including death, reported due to inappropriate  
13 prescribing. Since the implementation of the REMS,  
14 the number of reported events of interest have been  
15 consistently low. These include adverse events,  
16 medication errors, overdose, and accidental  
17 exposures. Beyond those little numbers, there have  
18 been no reports of adverse events due to  
19 inappropriate conversions.

20 These findings support the effectiveness of  
21 the program and reflect its strengths. One of the  
22 key strengths of the program is that it has

1 multiple mandatory elements for all stakeholders.  
2 Participation in the program is mandatory. No one  
3 may prescribe or dispense a TIRF medication outside  
4 this program. Every stakeholder must participate.  
5 Prescribers, patients, pharmacies, distributors,  
6 and manufacturers are all required to participate  
7 in the program.

8 Prescribers and pharmacies are required to  
9 undergo educational programs to enroll in the  
10 program and periodically are required to re-enroll  
11 with further education. Prescribers and pharmacies  
12 must be certified by completing a mandatory  
13 knowledge assessment. Every prescriber and every  
14 authorized pharmacy representative must score 100  
15 percent on this assessment in order to be  
16 certified.

17 Every two years, all prescribers,  
18 pharmacies, and patients must re-enroll in the  
19 program. And again, prescribers and pharmacy  
20 representatives must score 100 percent in order to  
21 be certified. Further, the prescribers and  
22 patients, and potentially the patients' caregivers

1 must sign the patient-provider agreement form that  
2 explicitly reviews the key educational elements and  
3 outlines their mutual obligations under the  
4 program.

5 Physicians must have this mutually signed  
6 the agreement prior to writing outpatient  
7 prescriptions for TIRF medication. They must also  
8 give the patients and/or caregivers the medication  
9 guide prior to writing the prescription. This  
10 process facilitates the required discussion of the  
11 safe use and risks of TIRF medications prior to  
12 prescribing.

13 This process has been working effectively.  
14 The program is designed as a closed system for all  
15 participants. This is to prevent any prescribing,  
16 dispensing, and distribution outside the system.  
17 There is continuous oversight and monitoring with  
18 the ability to take corrective actions as needed.  
19 This was all designed and monitored in  
20 collaboration with the FDA, and there's continuous  
21 improvements built into the design.

22 The program is built around the practice of



1 medicine fitting seamlessly into the clinical  
2 practice, existing opioid prescribing practices,  
3 and regulations. The TIRF REMS Access Program is  
4 included in the 2016 National Comprehensive Cancer  
5 Network guidelines for physicians who treat  
6 patients with cancer related pain.

7 It's also integrated directly into pharmacy  
8 processes since it's leaked into the existing  
9 pharmacy network that pharmacies use to process  
10 claims and report to insurance companies. Taken  
11 together, the evidence supports that there is an  
12 appropriate balance of access and restrictions.

13 The TIRF REMS Access Program ensures a safe  
14 and appropriate use of the TIRF medications with  
15 very low numbers of reported events of interest.  
16 There has been a substantial decrease in medication  
17 errors resulting in serious adverse events and  
18 death. The program has multiple mandatory  
19 requirements, including mandatory participation,  
20 education, certification, and a signed PPAF is  
21 required for every outpatient prescription. The  
22 program has undergone multiple refinements and

1 improvements since its initial implementation.  
2 There's additional work already planned and ongoing  
3 to further improve it all in collaboration with the  
4 FDA.

5 Stephen Sherman will now return to describe  
6 the current round of planned and ongoing  
7 improvements and to conclude this presentation.

8 **Industry Presentation - Stephen Sherman**

9 MR. SHERMAN: Thank you, Dr. Mariano.

10 Based on the results of the assessment  
11 reports and the ongoing collaboration with the  
12 agency, the TRIG has proposed improvements to the  
13 TIRF REMS Access Program's educational materials,  
14 and there's new studies with new data bases to  
15 augment the assessments of the effectiveness of the  
16 program.

17 To improve the educational materials for the  
18 TIRF REMS Access Program to ensure that they are  
19 conveying the necessary information concerning the  
20 safe use of TIRF, the TRIG is updating the  
21 information concerning starting continuous opioid  
22 treatment at least 1 week prior to the start of a

1 TIRF medication and to discontinue the use of TIRF  
2 when around-the-clock opioids are discontinued.

3 The TRIG will align the knowledge  
4 assessments and the KAB surveys with the revised  
5 education materials to measure stakeholder  
6 understanding and behavior. An additional revision  
7 that the TIRF is proposing to reinforce the use of  
8 TIRFs, that should be limited to only  
9 label-specific opioid-tolerant patients, is  
10 including prescriber attestations to the PPAF to  
11 confirm that the patient is opioid tolerant  
12 according to approved product labels.

13 The TRIG has also proposed the addition of  
14 attestation language to all pharmacy enrollment  
15 forms to allow the program to further audit  
16 inpatient pharmacies for REMS compliance. To  
17 address the number of noncompliant events, the TRIG  
18 is working with the FDA to further reduce and  
19 underscore the consequences of noncompliance with  
20 the program by applying the consequences earlier.  
21 The TRIG is also contacting healthcare  
22 professionals who have not re-enrolled to better

1 understand why they no longer prescribe TIRF.

2 To confirm the data reported in the RADARS  
3 report concerning the number of pediatric  
4 exposures, the TRIG is working to develop a  
5 protocol to analyze the data concerning TIRF use  
6 included in the drug involved mortality data and  
7 the Humedica database. TRIG is also working to  
8 validate the algorithm to identify label-specific  
9 opioid tolerance by assessing opioid tolerance in  
10 patients using data from both the inpatient and  
11 outpatient settings.

12 The TRIG is planning an evaluation of fatal  
13 and non-fatal overdose in label-specific tolerant  
14 patients versus those who are non-tolerant who  
15 start TIRF medications. Currently, the TRIG is  
16 working with the FDA to evaluate the potential data  
17 sources with a large enough safety population to be  
18 meaningful for this study. This study will  
19 leverage the results from the label-specific  
20 opioid-tolerant algorithm validation study.

21 In conclusion, the TIRF REMS has  
22 demonstrated the ability to assess that TIRF

1 medicines are generally being prescribed to  
2 appropriate patients in whom the benefits of these  
3 medications outweigh the risks. The product  
4 sponsors continue working with the FDA to ensure  
5 that the program evolves as we build on the  
6 progress made to address continuing areas of need.

7 TIRF medicines are an important component of  
8 the management of pain in opioid-tolerant cancer  
9 patients. Breakthrough cancer pain typically has  
10 an abrupt onset and rapidly becomes severe, but  
11 usually is of short duration. It's unpredictable,  
12 it's debilitating, and it's disruptive for  
13 patients, diminishing their quality of life.

14 The TIRF medicines are designed to meet the  
15 needs of cancer patients with breakthrough cancer  
16 pain. They have an immediate onset of action due  
17 to their transmucosal absorption. They are potent  
18 enough to manage severe pain, but also have a short  
19 duration of action that generally matches the  
20 duration of the pain.

21 The TIRFs are critical medications to treat  
22 breakthrough cancer pain. However, there are

1 significant risks associated with the use and  
2 misuse of TIRFs, including acute respiratory  
3 depression, which may lead to death. Thus, the TIRF  
4 REMS access program was designed to mitigate these  
5 risks.

6 Based upon the data provided to the agency  
7 in the annual reports, the TIRF REMS program has  
8 been effective in achieving its goals. Prior to  
9 its implementation, there were multiple reports of  
10 medication errors and inappropriate conversions  
11 resulting in serious adverse events and death.  
12 Since the implementation of the program, there have  
13 been no AEs reported in association with  
14 inappropriate conversions with the TIRF  
15 medications.

16 The available data indicate there are low  
17 numbers of overdose and pediatric and other  
18 inadvertent exposures. These data are supported by  
19 the independent data from RADARS. No program is  
20 perfect, and the TRIG and the FDA are working  
21 together to continually improve this program.

22 The TRIG is currently working with the FDA

1 to obtain real-world data from healthcare systems  
2 such as Henry Ford Health System and Humedica to  
3 complement the annual assessment reporting. The  
4 TRIG is also proposing to revise the pharmacy  
5 enrollment form to allow auditing for inpatient  
6 pharmacies. The TRIG is updating educational  
7 materials to address the issues of low-scoring KAB  
8 questions, and the TRIG is also proposing an  
9 attestation to the PPAF to remind prescribers of  
10 the need to restrict the use of TIRF to  
11 opioid-tolerant patients.

12 In conclusion, breakthrough cancer patients  
13 need TIRFs to adequately treat their severe and  
14 relatively short duration pain episodes. TIRFs are  
15 the only treatments specifically designed and  
16 approved for the indication of breakthrough cancer  
17 pain, which could otherwise be debilitating, life  
18 limiting, and cause high health care system  
19 utilization without appropriate treatment.

20 The TIRF REMS Access Program reduces the  
21 risk of the use of TIRFs without restricting access  
22 for the appropriate patients and must continue to

1 maintain that delicate balance. Thank you.

2 **Clarifying Questions**

3 DR. BATEMAN: Thank you.

4 Are there any clarifying questions regarding  
5 the industry presentations? Please remember to  
6 state your name for the record before you speak.  
7 If you can, please direct questions to a specific  
8 presenter.

9 Dr. Arfken?

10 DR. ARFKEN: My question is for Dr. Dart.  
11 It has to do with the RADARS system. You talked  
12 about that you could identify the medication. I  
13 was wondering about the comparison of other  
14 fentanyl products that you could identify as well;  
15 so potentially, large category of fentanyl when it  
16 could not be identified.

17 DR. SHERMAN: Dr. Dart?

18 DR. DART: Right. So the procedure in a  
19 poison center is to go through a procedure of  
20 identifying the product, for they ask the patient  
21 what it looks like, if there's any identifying  
22 features on it. And that helps a lot of the time.



1       You can't always tell because if the patient is  
2       found down, for example, then you don't know  
3       exactly what they got necessarily.

4               I think I have a slide for the fentanyl  
5       products as a whole.

6               Should I be seeing something? Slide up,  
7       please.

8               What we see here is on the vertical axis, a  
9       rate per 100,000 population and all of the quarters  
10      from actually all the way back from 2002 through  
11      2017. The Blue Line is total fentanyl, and that  
12      green line right below it is the fentanyl patch.  
13      Then down below you can see in whatever color that  
14      is, the dark color -- not the purple one -- that's  
15      the transmucosal product.

16              So the fentanyl cases are much higher for  
17      the patches than the transmucosal products. But  
18      when you add those lines together, they do hit the  
19      total. So we don't have a lot of misidentification  
20      here, it looks like, at least at the level of that  
21      patch versus transmucosal.

22              DR. ARFKEN: But for the treatment centers?

1 DR. DART: For the treatment center, this is  
2 self-identification. I don't have a slide on that.  
3 But for the treatment centers, they get a form.  
4 The form has 4 sides, 2 pages/2 sides. And they  
5 scan that and endorse all the products that they  
6 have abused in the past 30 days.

7 We've looked at that to try to understand  
8 whenever you use a paper form, especially, but  
9 really with any survey, you can get this concept of  
10 careless endorsements where a person just endorses  
11 things because they're filling out a questionnaire,  
12 and that can have all kinds of different  
13 motivations.

14 As an example, slide up please, this shows  
15 the number of endorsements on the vertical axis for  
16 the TIRF products and the comparators pre and post.  
17 What you see here is the TIRF products do have a  
18 higher proportion of what we call careless  
19 responses. That does have an effect. It actually  
20 lowers the amount, the number of endorsements, for  
21 the TIRF products.

22 If you put up slide 2 here, please. I want

1 to make it clear as I'm going through this that the  
2 FDA has a presentation on this that comes after.  
3 And I don't think they've seen this slide, so just  
4 so you understand, this is an accurate slide but it  
5 is different.

6 This slide shows on the left the rate per  
7 100,000 population for the TIRF products before and  
8 after the REMS was initiated, and on the right  
9 shows that the same numbers after careless  
10 responses were removed. One of the interesting  
11 things here is that some of that increase I showed  
12 in my core presentation about increasing TIRF cases  
13 towards the end of the surveillance period actually  
14 goes away when you take away the careless  
15 responses.

16 I'm not sure how far to go with this  
17 because, as I said, there's a presentation by FDA,  
18 and I can answer more questions than as well, I  
19 believe.

20 DR. BATEMAN: Dr. Staffa wanted to make a  
21 comment.

22 DR. STAFFA: Yes. This is Judy Staffa.

1 Thank you, Dr. Dart.

2 This is a finding -- just to back up, many  
3 sponsors contract with RADARS to get data to look  
4 at the misuse and abuse of their products. FDA  
5 also has a contract with RADARS to examine patterns  
6 of misuse and abuse.

7 We had a public meeting last summer trying  
8 to understand some of the scientific concerns about  
9 available data and to try to understand how we  
10 might improve the situation. As a result of that  
11 meeting, we awarded a contract to RADARS to delve  
12 into the quality of the reporting that we see from  
13 people coming into treatment centers and reporting  
14 on these questionnaires what they're abusing. We  
15 just wanted to learn more, try whether people are  
16 able to report things accurately, and what factors  
17 might influence that.

18 So as we were preparing for this advisory  
19 committee, we used our contract with the RADARS  
20 data, which you'll hear about from Dr. Radin, to  
21 look at some of the product-specific rates of  
22 abuse. We were concerned about some of the

1 patterns we saw. We didn't really understand them,  
2 so we had followed up with the RADARS folks to try  
3 to talk to them and learn more. And the results of  
4 this extra work that FDA had going on, not just  
5 about TIRFs but more generically across all  
6 products, actually had come to fruition. And we  
7 just learned about these findings literally last  
8 week.

9 So given that these findings about what  
10 Dr. Dart refers to as careless responders, and were  
11 actually identified through FDA work with the  
12 contract, we've incorporated some of that into our  
13 own slides. And of course, Dr. Dart, who knows  
14 much more about it even than we do, is here to be  
15 able to add an answer questions. And that's where  
16 these additional slides have come from, is that  
17 work for FDA.

18 So if I haven't totally confused you,  
19 perhaps we'll continue to confuse you more as this  
20 goes on.

21 DR. DART: I'm sorry. I figure it's the  
22 first question brought up that issue.

1 DR. STAFFA: Correct. And I think it's  
2 appropriate for him to try to address that as fully  
3 as possible.

4 DR. BATEMAN: Dr. Kulldorff?

5 DR. KULLDORFF: I have three questions for  
6 Dr. Stemhagen and two for Dr. Dart. We'll start  
7 with Dr. Stemhagen maybe. The first one is the  
8 TIRFs that are indicated for cancer patients, you  
9 showed, for example, what proportion were  
10 prescribed to people who are not opioid tolerant.

11 Do you know what is the percentage that were  
12 prescribed to non-cancer patients versus cancer  
13 patients? That's my first question.

14 My second question is on slide CC-59, it  
15 says that 86 percent of outpatient prescriptions  
16 that had an opioid use, it was 14 percent there  
17 that would be considered non-tolerant to opioids,  
18 but then on the next bullet it's 42 percent. So I  
19 assume that includes those 14 percent, but what are  
20 those 28 percent that had an opioid but are still  
21 considered to be opioid non-tolerant?

22 My third question is on slide CC-66 with the

1 spontaneous reports, this shows reports where TIRF  
2 was one of the drugs, but I assume that many of  
3 these reports have other drugs as well. For  
4 example, it could be chemotherapy, and therefore  
5 the report, maybe somebody was thinking that the  
6 chemotherapy might have caused the adverse event.

7 So the question there is do you have  
8 information on those numbers in terms of other drug  
9 uses in those reports, for other drugs?

10 DR. SHERMAN: I'll answer your first  
11 question concerning do we know -- unfortunately, we  
12 don't capture in the access program, we don't  
13 capture -- in the TIRF REMS Access Program, we  
14 don't capture the diagnosis associated with the  
15 prescription, so we do not have a breakdown of  
16 cancer patients versus non-cancer patients.

17 DR. KULLDORFF: Thank you.

18 DR. SHERMAN: And I'll let Dr. Stemhagen  
19 answer your second two questions.

20 DR. KULLDORFF: Thank you.

21 DR. STEMHAGEN: Thank you. Just to add to  
22 that, when we were able to -- for some of the data

1       that I showed, for instance, with the deaths, that  
2       we could see that some of them were -- for  
3       breakthrough cancer pain where the patient had  
4       cancer, we noted it. But unfortunately, in many  
5       data sources, the information is just not  
6       available. But there's no standard way that we  
7       capture that.

8               If you don't mind, I'll answer your third  
9       question because the second question really should  
10      go to Dr. Phillips.

11             DR. KULLDORFF: Okay.

12             DR. STEMHAGEN: So your third question was  
13      concerning the spontaneous reports. If I can have  
14      this slide up, slide 2?

15             DR. KULLDORFF: Yes, if there is information  
16      about other drugs that are a part of those reports.

17             DR. STEMHAGEN: Yes. When there is  
18      information, the person taking the call usually  
19      tries to capture that information. We do not have  
20      a slide on that. And unfortunately, again, as we  
21      note, not only that the 355 had information,  
22      insufficient causality assessment, part of that



1 would have been looking at the other concomitant  
2 medications.

3 Spontaneous reports sort of are notorious  
4 for having limited information, so we don't have  
5 any standard way that we have looked at it. The  
6 only way that we do have here is that 187 of those  
7 deaths were determined not to be related to the  
8 TIRF medicines. There was another attribution  
9 indicated by the reporter and that there were  
10 several that the reporter specifically said it was  
11 a TIRF medicine, not something else, but it's not  
12 standard information.

13 So the questions about the opioid tolerance  
14 study, I'm going to turn that over to Dr. Phillips.

15 DR. PHILLIPS: I am Syd Phillips, and I am  
16 from IQVIA. Could you repeat your question,  
17 please, about the opioid tolerance study?

18 DR. KULLDORFF: This is from slide CC-59, so  
19 maybe if somebody can put it up on the screen.

20 DR. PHILLIPS: Slide up, please.

21 DR. KULLDORFF: So it says there that  
22 86 percent had an opioid prescription, so I assume

1       that means that 14 percent did not, which means  
2       that will be opioid non-tolerant. But then on the  
3       next bullet, it says 42 percent, so there's a  
4       different definition used in these two bullets.

5               So what explains those two different numbers  
6       of 14 percent versus 42 percent?

7               DR. PHILLIPS: Thank you. For the  
8       86 percent, that's just the proportion of patients  
9       who had a prescription for an opioid prior to the  
10      initial TIRF. That assessment does not include  
11      whether or not those patients are opioid tolerant  
12      or non-tolerant.

13              The 42 percent of those patients who have  
14      prescriptions for opioids prior to the initial  
15      TIRF, were they opioid tolerant or non-tolerant,  
16      and that's the 42 percent who had 7 days or more of  
17      sufficient dose immediately proceeding the initial  
18      TIRF.

19              But of all the patients included in this  
20      study who had an initial TIRF, 86 percent had  
21      filled a prescription for an opioid in the 30 days  
22      prior to. So it's not necessarily opioid

1 tolerance.

2 DR. KULLDORFF: So 42 percent used an  
3 additional 7 days prior.

4 DR. PHILLIPS: Yes. And then some of those  
5 86 went on to be opioid tolerant or not.

6 DR. KULLDORFF: Okay. Thank you.

7 DR. BATEMAN: Do you have additional details  
8 on that 42 percent in terms of the characteristics  
9 of their opioid fills, the duration, the amounts  
10 that they're on? Is it that they're just missing  
11 the 60 milligrams of morphine equivalent  
12 thresholds, or has that group been characterized  
13 more fully?

14 DR. PHILLIPS: We did not characterize that  
15 group more fully in that study.

16 DR. BATEMAN: Dr. Nelson?

17 DR. SHERMAN: That's actually -- just in  
18 response to your question, we're doing a validation  
19 study of the 42 percent. I believe that's one of  
20 the issues that we're trying to address.

21 DR. KULLDORFF: And I also had two questions  
22 for Dr. Dart, if that's okay.

1           On slide CC-82, it lists that 0.5 per 10,000  
2       prescriptions have intentional abuse. And then on  
3       slide CC-91, it says that about 40 per 10,000 has  
4       an abuse of the TIRF products. So it's 0.5 for  
5       intentional abuse and 40 for abuse. What's the  
6       definition of the difference with the intentional  
7       abuse and abuse?

8           DR. DART: That's a good question. I may  
9       take a second here to sort this out.

10          I think we should look at this and come back  
11       with an answer because I see a couple  
12       inconsistencies on the slides that don't fit. So  
13       I'll need to -- oh, I think we're talking about two  
14       different programs here. The slide here is the  
15       treatment centers that you're seeing and the  
16       previous slide you refer to as poison centers.

17          DR. KULLDORFF: Oh, okay. Thank you.

18          DR. DART: That's an easy mistake.

19          DR. KULLDORFF: Thank you. The last  
20       question is on slide CC-94, it says what the  
21       prevalence is for non-medical use by college  
22       students. What was the unit of that about

1 prevalence? It's about 2 for the TIRF. Is that to  
2 2 per --

3 DR. DART: Two percent.

4 DR. KULLDORFF: Two percent of college  
5 students.

6 DR. DART: Thank you. Yes.

7 DR. KULLDORFF: Thank you.

8 DR. BATEMAN: Dr. Nelson?

9 DR. NELSON: Thanks. Lewis Nelson from  
10 Rutgers. I have two questions if I can; one for  
11 Dr. Pergolizzi about his slide CC-9, which stated  
12 that -- in modification 2, it stated that you  
13 revised the attestation of physicians in patients  
14 to address concerns of patient access.

15 Could you provide some clarity to that?  
16 What was the problem that you were addressing?  
17 Because it seems like most of what we did was  
18 reduce the specificity of who we're prescribing  
19 for, and I'm not sure I understood how that  
20 addressed patient access issues and what the access  
21 issues were.

22 DR. SHERMAN: That's really not a

1 Dr. Pergolizzi question. I'll bring up Amanda  
2 Bulkley from McKesson who will hopefully address  
3 your question.

4 (Pause.)

5 DR. SHERMAN: Sorry. I'm getting new  
6 information. Kyle Irwin is going to be answering  
7 that question.

8 MR. IRWIN: Yes. I believe that  
9 modification to the patient prescriber agreement  
10 form was based on feedback we were  
11 receiving directly from prescribers in the call  
12 center and not being able to fully attest to the  
13 form. So we submitted that changed proposal to  
14 update the language that would make those  
15 prescribers more comfortable.

16 DR. NELSON: So just so I understand it,  
17 before you said my patient is opioid tolerant and  
18 now we say I understand that opioid tolerance is  
19 important, essentially. It's not clear to me how  
20 that made access any better. It just seemed like  
21 it changed the thresholds for prescribing. No?

22 MR. IRWIN: It might not have been the

1 perfect response at the time --

2 DR. NELSON: Okay, then that's fine.

3 MR. IRWIN: -- and we've learned our lesson,  
4 and maybe that's why we're going back.

5 DR. NELSON: Okay. No, that's fine. If I  
6 could also just ask a question of Dr. Stemhagen.  
7 On your slide CC-48, you say the decline in the  
8 numbers of prescriptions is primarily due to  
9 enrollment expiration without re-enrollment. But  
10 if you go to the previous slide, CC-47, it looks  
11 like everybody's re-enrolling, but the numbers of  
12 prescriptions are going down anyway.

13 Enrollment, I assume, is that purple line  
14 that looks at the prescriber's re-enrollment. So  
15 there's got to be a different explanation than  
16 expiration of enrollment. Do we have a reason that  
17 they're prescribing less often? Does it come down  
18 to the access issue I just raised before?

19 DR. STEMHAGEN: Actually, Amanda from  
20 McKesson can answer that. That was a survey that  
21 was done by McKesson outreaching to prescribers who  
22 did not re-enroll.

1 MS. BULKLEY: Good morning. My name is  
2 Amanda Bulkley. I'm with McKesson, and we are the  
3 REMS administrator for the TIRF REMS Access  
4 Program. We did do an outreach to just a subset of  
5 prescribers and pharmacies that deactivated during  
6 a certain assessment period to determine why they  
7 were not re-enrolling, as the number one reason was  
8 just enrollment exploration.

9 If I can get slide 2? We did determine from  
10 that outreach that it was primarily due to no  
11 longer having patients to dispense products to or a  
12 change in prescribing activity.

13 What we do plan to do is an additional  
14 outreach to further drill down and get more subset  
15 reasons out of that to determine if REMS is a  
16 barrier or media access, or if there's any other  
17 deterrent that is causing the prescribers and  
18 pharmacies to not re-enroll.

19 DR. NELSON: If I could just follow up  
20 quickly. The prescribers are re-enrolling, right?  
21 I mean that line's not exactly flat, but it's not  
22 falling as much as the other two are. So it just



1       sounds like they're prescribing less. They're  
2       enrolling the docs, but they're prescribing less.

3               MS. BULKLEY: The prescription has dropped  
4       as well as the enrollment counts for prescribers  
5       over time.

6               DR. NELSON: Not really according to that  
7       picture, but okay.

8               DR. SHERMAN: Dr. Pergolizzi, do you --

9               DR. BATEMAN: I think we'll stop here and  
10      take a 10-minute break. We should have additional  
11      time after the open public hearing for additional  
12      clarifying questions for the industry  
13      presentations.

14              As a reminder to panel members, please  
15      remember there should be no discussion of the  
16      meeting topic during the break amongst yourselves  
17      or with any members of the audience. We'll resume  
18      at 10:35.

19              (Whereupon, at 10:27 a.m., a recess was  
20      taken.)

21              DR. BATEMAN: We'll now proceed with FDA  
22      presentations, Dr. Auth.

**FDA Presentation - Doris Auth**

DR. AUTH: Good morning. My name is Doris Auth from the Division of Risk Management, and I'll be discussing some of the findings from the FDA review of the TIRF REMS assessments. I'll begin with some very brief background on REMS assessments and provide an overview of the TIRF REMS assessment metrics, and then specifically discuss the key findings from our evaluation of TIRF REMS utilization, operations, and surveys.

I'll also point out some potential indicators of barriers to patient access and burden on the healthcare delivery system that may be related to the TIRF REMS. Following my presentation, Dr. Rose Radin, from the Division of Epidemiology, will provide the FDA review of the epidemiology and surveillance data.

Before I present the findings on the TIRF REMS assessments, I would like to spend a minute on some general REMS assessment challenges.

Evaluation of REMS may be challenged by a number of issues. On this slide, we'll only describe those

1       that are pertinent to the TIRF REMS. First, drugs  
2       with REMS may be for orphan or other small patient  
3       populations, or the drug may be indicated as second  
4       or even third-line therapy, all of which result in  
5       low utilization.

6               Next, nearly every REMS has an educational  
7       component, and surveys of knowledge may not be  
8       representative of the patient, pharmacist, or  
9       prescriber population. Also, outcomes of interest  
10      may be difficult to monitor through spontaneous  
11      reports or other data sources.

12             Finally, whenever epidemiology or other  
13      studies are required to evaluate a REMS, additional  
14      time may be necessary for protocol development, FDA  
15      review, and comment and agreement with industry.  
16      This may impact the timeliness of the studies. We  
17      attempt to overcome these challenges by using  
18      multiple data sources, multiple metrics, and  
19      surrogates.

20             Once again, these are the goals and  
21      objectives of the TIRF REMS, and I'm not going to  
22      read through them again. I would like to point

1 out, however, that all REMS are designed with the  
2 intent that the requirements of the REMS will allow  
3 the goals and objectives to be met, and that this  
4 will be done while minimizing burden on the  
5 healthcare delivery system and not creating  
6 unnecessary barriers to appropriate patient access  
7 to the drug.

8 The REMS assessment plan is developed prior  
9 to REMS approval and frequently revised following  
10 the review of a REMS assessment. It should include  
11 both measures of the REMS processes or operations,  
12 as well as the impact of the program on outcomes of  
13 interest, which are tied to the goals and  
14 objectives, and there may be overlap in some of  
15 these measures.

16 For the TIRF REMS, measures of REMS  
17 processes include data from both the TIRF REMS  
18 database of enrollment, as well as external  
19 utilization sources that were accessed by the FDA,  
20 dispensing data from these same sources and  
21 compliance with REMS requirements for certification  
22 and safe use. The evaluation of outcome also

1 includes enrollment and utilization data since this  
2 may signal issues with burden or access. It also  
3 includes results from surveys of knowledge of  
4 patients, pharmacists, and prescribers.

5 My colleague, Dr. Rose Radin, will discuss  
6 the estimates of TIRF use in opioid non-tolerant  
7 patients, the estimate of frequency with which  
8 patients switch between TIRF products, as well as  
9 the evaluation of adverse events from both  
10 spontaneous reports and other surveillance data.

11 The first metric I'll discuss is the  
12 evaluation of TIRF utilization trends. Earlier  
13 today, the TRIG provided utilization from their  
14 database of prescribers, pharmacies, and patients.  
15 The FDA also reviewed outpatient retail utilization  
16 of TIRFs in the two years prior to REMS approval  
17 through 2017 based on prescription dispensing data  
18 from retail pharmacies.

19 This first graph shows an estimate of  
20 prescriptions dispensed for all opioid analgesics  
21 from outpatient retail pharmacies over the study  
22 period shown by the blue bars. In 2010, there were

1 approximately 250 million prescriptions for opioid  
2 analgesics, which had fallen to around 200 million  
3 in 2017. In comparison, prescription for TIRF  
4 medicines, shown by the solid red line on the  
5 X-axis, don't even register on the scale.

6 I'd like to draw your attention to the text  
7 in the red circle that states, "In 2017, TIRF  
8 medicines accounted for only 0.02 percent of total  
9 prescriptions dispensed for opioid analgesics."

10 The last point from this slide is that overall  
11 opioid analgesic prescriptions began to decline  
12 around 2013.

13 This next graph of only TIRF prescriptions,  
14 which are shown in the light gray bars and only in  
15 the thousands, shows that prescriptions for these  
16 products began declining earlier than those for all  
17 opioid analgesics. The decline began prior to the  
18 implementation of the TIRF REMS.

19 After the drop in 2012, prescriptions for  
20 all TIRF medicines appear to seem flat. However,  
21 looking at the individual product lines,  
22 prescriptions for all but one of the TIRF products

1       either remain very low or continue to decline. And  
2       in 2017, just under 40,000 prescriptions for TIRF  
3       products were dispensed. This represents a 76  
4       percent decrease in dispensing from 2010 through  
5       2017.

6               The last graph from the utilization data  
7       shows the use of TIRF medicines based on patient  
8       data obtained from outpatient retail pharmacies.  
9       Similar to prescription dispensing data, the total  
10      number of patients dispensed a TIRF medicine, shown  
11      by the dotted bars, decreased by 80 percent for  
12      approximately 24,000 patients in 2010 to just under  
13      5,000 patients in 2017.

14              The utilization data also provides some  
15      insight on TIRF prescriber specialties. In 2017,  
16      the top prescriber specialties for TIRF medicines  
17      for anesthesiologists and pain management  
18      specialists at 34 percent, followed by nurse  
19      practitioners and physicians' assistants at 15  
20      percent; and then physical medicine and  
21      rehabilitation and family or internal medicine.  
22      Prescribing by both oncologists and neurologists

1 was under 10 percent. Other specialties or those  
2 not documented were 16 percent. Unfortunately,  
3 specialty is not available for the non-physician  
4 prescribers from this data source.

5 We have very limited diagnosis data for  
6 patients receiving TIRF medicines. The diagnosis  
7 data shown on this slide are obtained from surveys  
8 of a sample of 3200 prescribers, office-based  
9 physicians who report on patient activity during  
10 one day per month.

11 Consistent with prescription dispensing data  
12 described in the previous slide, the use of TIRF  
13 medicines from this data source was also low. Pain  
14 specialists were the only specialists that  
15 mentioned using a TIRF, and this was for a  
16 diagnosis of pain, not otherwise specified, pain  
17 related to cancer conditions, and abdominal and  
18 pelvic pain.

19 Since there is no specific diagnosis code  
20 for breakthrough pain related to cancer, it's  
21 unclear if the other non-cancer conditions could  
22 have also been breakthrough pain. I should also



1 point out that these survey data are not linked to  
2 dispense prescriptions. They only provide some  
3 insight on prescriber intent. As well, the data do  
4 not provide any information on whether the patients  
5 were opioid tolerant.

6 The utilization data, similar to what the  
7 TRIG presented earlier, shows low overall use of  
8 TIRF medicines with the top prescriber specialty  
9 being pain specialists and anesthesiologists.

10 We're interested in learning what may be driving  
11 the decrease in utilization of these products.

12 Additional information on practice sites and  
13 indication for use might further our understanding  
14 of TIRF prescriber specialties and the types of  
15 pain the TIRF medicines are being used to treat.

16 The FDA has already stated that the TIRF  
17 REMS is operating as intended, but there are a few  
18 observations from the operations data that I'd like  
19 to highlight. I'd first like to point out, as the  
20 sponsors did, that the majority of prescriptions  
21 for TIRF medicines, 92 percent, are authorized by  
22 the REMS, meaning the prescriber, pharmacy, and

1 patient are enrolled, and the prescription can be  
2 dispensed once any additional required insurance  
3 approval is received.

4 A very small percentage of these, about  
5 3 percent, are authorized after an initial REMS  
6 rejection, which is most frequently related to a  
7 missing patient provider agreement form.

8 Approximately 8 percent of TIRF prescriptions are  
9 never authorized by the REMS. We have no further  
10 information on whether those patients go on to  
11 receive another prescription that is authorized by  
12 the REMS or if another opioid analgesic is  
13 prescribed in place of a TIRF.

14 The number of TIRF prescriptions that are  
15 dispensed without receiving a REMS authorization  
16 has been very low, however, these events are all  
17 self-reported. The TRIG is working on an audit  
18 process to more actively identify additional  
19 episodes.

20 Despite the majority of prescriptions being  
21 authorized by the TIRF REMS, we've noticed, as the  
22 TRIG pointed out as well, that the enrollment of

1       prescribers, and to a lesser extent, pharmacies,  
2       has been declining. Over the past three  
3       assessments, there's been a 30 percent decrease in  
4       enrolled prescribers, from around 9100 in and the  
5       48-month assessment down to 6600 in the most recent  
6       or 72-month assessment.

7               I'm not going to cover the outreach that the  
8       TRIG conducted. I believe that they covered that  
9       really well. I would just like to say that we  
10      agree that additional details are needed to fully  
11      understand the factors underlying the decision by  
12      prescribers or pharmacies to not enroll in the  
13      REMS. The decrease in enrollment may signal a  
14      potential patient access issue if there are no  
15      enrolled prescribers available in a particular  
16      geographic area. It also may signal a potential  
17      issue of burden to the prescribers and pharmacies.

18             Re-enrollment of pharmacies has not declined  
19      as sharply as prescribers, however, we've noted  
20      that of the nearly 42,000 chain retail pharmacy  
21      stores and 6600 independent pharmacy stores that  
22      have ever enrolled in the TIRF REMS, the majority

1 of the dispensing is actually occurring in the  
2 independent pharmacies, which account for 65  
3 percent of TIRF dispensing.

4 At the end of the 72-month assessment  
5 period, there were just under 38,000 chain retail  
6 pharmacies and around 3800 independent retail  
7 pharmacy stores that remain enrolled in the TIRF  
8 REMS. So only 43 percent of the independent  
9 pharmacies that handle the majority of the  
10 dispensing have re-enrolled in the REMS. These  
11 dispensing observations are concerning as they may  
12 also signal a potential barrier to appropriate  
13 patient access.

14 So while it does appear that the REMS  
15 processes are functioning to ensure prescribers for  
16 the TIRF medicines are written by certified  
17 prescribers, the decreasing prescriber and pharmacy  
18 enrollment is concerning. The reasons for this are  
19 unclear, and they may negatively impact a patient's  
20 ability to receive a TIRF prescription. Again, the  
21 TIRF REMS assessment requires surveys of knowledge  
22 to assess prescriber, pharmacist, and patient

1 understanding of the risk and safe use of TIRFs.

2 First, a little bit of background on REMS  
3 assessment surveys. Most often, these are cross  
4 sectional surveys of prescribers, pharmacists, and  
5 patients. Typically, the FDA has the opportunity  
6 to review the survey methodology and provide  
7 recommendations that the sponsor can incorporate  
8 into the surveys prior to fielding. We recommend  
9 that all sponsors conduct pre-testing or  
10 qualitative testing of their surveys before  
11 implementation.

12 We also ask sponsors to set target knowledge  
13 rates. While there is no standard for this rate  
14 and it may differ depending on the stakeholder  
15 being surveyed or the safety message, in the  
16 majority of instances, it's 80 percent. We  
17 currently have an FDA guidance in development to  
18 address survey design issues.

19 I'm going to skip this slide. I believe  
20 that the TRIG covered the eligibility and  
21 recruitment for the surveys. So moving on to the  
22 key findings and gaps in the surveys, as already

1 presented by the sponsors, survey respondents have  
2 shown consistently high knowledge across each of  
3 the 6 survey waves. Patient, pharmacists, and  
4 survey respondents were aware that patients should  
5 be opioid tolerant prior to taking a TIRF medicine.  
6 However, knowledge has been a bit lower for a  
7 couple of specific TIRF questions.

8 The first of these is a TIRF administration  
9 question also pointed out by the TRIG, which was  
10 that if a patient stops taking there  
11 around-the-clock opioid, they must also stop taking  
12 the TIRF. Now roughly, only 40 percent of patients  
13 and pharmacists were able to answer this question  
14 correctly.

15 Another question with lower knowledge, which  
16 I apologize is not on the slide and again pointed  
17 out by the TRIG, was this question about whether  
18 chronic non-cancer pain is an appropriate  
19 indication for the use of TIRF medicines. The  
20 knowledge for this was lower in prescribers ranging  
21 from 50 percent to nearly 80 percent, with more  
22 higher knowledge noted in the past couple of

1 surveys.

2 In terms of gaps or survey limitations, the  
3 response rate for the TIRF surveys was low, calling  
4 into question the representativeness of the  
5 results. There were significant differences  
6 between the surveyed population and the general  
7 population of TIRF patients, prescribers, and  
8 pharmacists on characteristics such as education,  
9 ethnicity, the average time per month TIRF medicine  
10 was prescribed, as well as the type of pharmacy  
11 where the pharmacists practice. Because of these  
12 differences, we were concerned that the results  
13 were not generalizable.

14 For the most recent survey, we asked that  
15 the TRIG provide a subgroup analysis and conduct a  
16 sensitivity analysis to predict the knowledge rate  
17 in all users adjusting for these characteristics.  
18 Overall, the subgroup analysis did not show a  
19 systematic bias in the standardization of the  
20 results and did not change the main conclusions.

21 As will be discussed in the next  
22 presentation, the amount of TIRF prescribing to

1 patients who are not opiate tolerant conflicts with  
2 the high knowledge rate. We acknowledge that this  
3 may be related to prescribers' clinical experience  
4 with these products.

5 In summary, the TIRF medicines represent a  
6 very small portion of the overall opioid market.  
7 They are prescribed to very low numbers of  
8 patients. The TIRF REMS has been implemented as  
9 intended and continues to function to ensure that  
10 prescribers and pharmacists are educated and  
11 enrolled in the REMS prior to prescribing or  
12 dispensing and that patients are counseled on the  
13 risks and safe use of the product.

14 Overall, with some exception, patients,  
15 prescribers, and pharmacists surveyed showed high  
16 knowledge of TIRF risk and safe-use practices.  
17 Both utilization of TIRF medicines and enrollment  
18 in the TIRF REMS is declining, and the impact of  
19 the declining utilization may lead to reduced  
20 access for patients.

21 Thank you. The next presentation will be  
22 the FDA review of the epidemiologic and



1 surveillance data from the TIRF REMS assessments.

2 **FDA Presentation - Rose Radin**

3 DR. RADIN: Good morning. I am Rose Radin.  
4 I'm an epidemiologist with the Division of  
5 Epidemiology. Here again are the TIRF REMS, goals,  
6 and objectives. Objective 4 was covered in the  
7 previous talk by Dr. Doris Auth. This talk will  
8 cover epidemiologic and surveillance data for  
9 objectives 1 to 3 and the goals.

10 The presentation agenda is for each  
11 objective and REMS goal, the sponsor submission,  
12 FDA generated analysis, development of new studies  
13 by the sponsors, and conclusions from our review, I  
14 will conclude the presentation with an overall  
15 summary, starting with objective 1, which is  
16 prescribing and dispensing TIRF medicines only to  
17 appropriate patients, which includes use only in  
18 opioid-tolerant patients.

19 The review of data for objective 1 covers  
20 the sponsor's submission, FDA generated analyses of  
21 FAERS, development of new studies by the sponsors,  
22 and conclusions from our review. As you can see,

1       there is a lot of material, and it will take some  
2       time to complete.

3               On to the sponsor's submission. The  
4       sponsor's estimated the prevalence of prior opioid  
5       tolerance among patients starting TIRFs. They  
6       conducted a pharmacy claims-based study in the  
7       IQVIA longitudinal prescription database 2012 to  
8       2015.

9               Opioid tolerance was determined by a  
10       claims-based algorithm that calculated average  
11       daily dose from the prior opioid prescriptions  
12       recorded dosage unit strength and days' supply.  
13       The criterion for opioid tolerance was a minimum  
14       average daily dose for the 7 days before the TIRF  
15       prescription. The dose thresholds are provided at  
16       the bottom, the same as were presented previously.

17              How prevalent is opioid tolerance? The  
18       study estimated 58 percent of all patients starting  
19       a TIRF medicine were opioid tolerant. Estimates  
20       were 45 to 65 percent in product-specific analyses,  
21       including sensitivity analyses. However, one  
22       sponsor conducted an alternative analysis with an

1 algorithm that estimated 77 percent opioid  
2 tolerance, not 58 percent, using a similar data  
3 source. The sponsors then compare the two  
4 algorithms' methods and concluded the algorithm  
5 that estimated 77 percent opioid tolerance had no  
6 criterion for prior opioid dose. It simply counted  
7 7 days supply of an opioid at any dose, which means  
8 it overestimated opioid tolerance.

9           Given the low prevalence of opioid  
10 tolerance, FDA sought more information. These  
11 medicines are contraindicated in opioid  
12 non-tolerant patients due to the risk of fatal  
13 respiratory depression, so we looked for deaths  
14 that were reported involving TIRF medicines. We  
15 also looked for adverse events reported in opioid  
16 non-tolerant patient. Furthermore, we wanted to  
17 examine the accuracy of the claims-based algorithm  
18 for opioid tolerance.

19           It's possible that the estimated 58 percent  
20 opioid tolerance could be an underestimate if there  
21 were substantial prior opioid exposures such as  
22 from inpatient and specialty pharmacy setting,

1       which the claims-based algorithm may have failed to  
2       capture. There may also be limitations to  
3       ascertaining prior opioid dose from claims data.  
4       FDA had conducted several previous studies with  
5       similar findings of a parent prescription of high  
6       potency opioid products to opioid non-tolerant  
7       patients, so we were already questioning the  
8       validity of claims-based algorithms and conducted a  
9       validation study, which will be presented later.

10             In order to evaluate the most serious  
11       outcome of TIRF medicine use in opioid non-tolerant  
12       patients, we are now transitioning to a review of  
13       fatal outcomes in spontaneous report data. This  
14       slide depicts the sponsor's data for all fatal  
15       outcomes in the reported time periods. We know  
16       deaths are expected to occur in patients with  
17       cancer pain, which is the indication for TIRF  
18       medicines.

19             Earlier, the sponsors presented their data,  
20       which showed 549 deaths reported between August  
21       2016 through August 2017 in all patients  
22       irrespective of opioid tolerance status. This

1 represents an increased number of deaths compared  
2 to previous reporting period. This is concerning  
3 to us given known risks of TIRF medicines, concern  
4 for use by opioid non-tolerant patients, and drug  
5 utilization data showing decreasing use of TIRF  
6 medicines.

7 The sponsors noted that 65 percent of these  
8 cases lacked sufficient information for causality  
9 assessment. Of the remaining cases, only 7 were  
10 judged by the sponsors to be related or possibly  
11 related to a TIRF medicine. No additional details  
12 were provided for these 7 cases, including details  
13 to assess opioid tolerance.

14 Because of the TIRF REMS, the sponsors have  
15 more contact with prescribers and patients than  
16 they otherwise would if the REMS were not in place.  
17 This contact occurs through re-enrollment  
18 activities and surveys from which they have the  
19 chance to become aware of adverse events, including  
20 death.

21 For example, a prescriber may receive a call  
22 to update the PPAF form for enrollment of a

1 patient. When they make the sponsor aware, the  
2 patient is deceased or a family member may receive  
3 a survey and inform the sponsor the patient is  
4 deceased.

5 Thus, the Division of Pharmacovigilance  
6 evaluated FAERS data in an attempt to better  
7 characterize the reported adverse events with TIRF  
8 medicines given safety concerns for respiratory  
9 depression and death. The following FAERS analysis  
10 is not included in the FDA background package.

11 FDA reviewed FAERS cases with a fatal  
12 outcome for the same reporting period as the  
13 sponsors, August 2016 through August 2017. We  
14 initially retrieved 1,289 reports. In an effort to  
15 determine whether there were fatalities due to the  
16 use of a TIRF medicine, we excluded reports that  
17 were generated from the medical literature that  
18 mentioned fentanyl in general rather than a  
19 specific TIRF medicine, bringing the number of  
20 reports to 532. After further exclusions listed on  
21 this slide, including a substantial number noting  
22 progression of the cancer, we were left with 308

1 cases.

2 This slide lists the descriptive  
3 characteristics of the 308 fatal cases we reviewed  
4 in more detail. The reason for use, 43 percent was  
5 for cancer pain and 52 percent was not reported.  
6 When concomitant opioid medications were provided,  
7 there was a lack of detail such as dose, frequency,  
8 or formulation to assess opioid tolerance.

9 Although 18 percent of the reports report  
10 concomitant opioids, we would expect it to be  
11 higher in patients prescribed a TIRF medicine for  
12 cancer pain. What we begin to see here is a trend  
13 of missing information. In general, many reports  
14 in the FAERS database commonly are characterized by  
15 missing and incomplete information. This is an  
16 important limitation of spontaneous adverse event  
17 data.

18 Continuing the table, this slide shows that  
19 94 percent of the cases did not include a cause of  
20 death. The one case of accidental overdose  
21 occurred in an adult with a history of illicit drug  
22 abuse, and the one fatality attributed to

1 respiratory depression occurred in a patient who  
2 potentially may have abused or misused the TIRF  
3 medicine. The most commonly reported TIRF  
4 medicines in our case series were sepsis followed  
5 by oral transmucosal fentanyl citrate and Fentora,  
6 which is generally consistent with the drug  
7 utilization data.

8 Next, using a focused search, we evaluated  
9 the FAERS database for reports of opioid  
10 non-tolerance reported between 2010 through 2017.  
11 We identified 10 cases of adverse events in opioid  
12 non-tolerant patients taking TIRF medicines. The  
13 adverse events are listed on this slide by system  
14 organ class. They include somnolence, dizziness,  
15 and euphoria, among other labeled events. The  
16 adverse events are generally not indicative of  
17 overdose or respiratory depression, and there were  
18 no deaths.

19 Overall, the nature and severity of the  
20 reported adverse events are consistent with the  
21 known safety profile of TIRF medicines. We  
22 acknowledge the small number of cases and present



1       these data to give you an idea of the adverse  
2       events that have been reported to us. If opioid  
3       tolerance is not explicitly stated, we need more  
4       information to assess non-tolerance, but these  
5       reports do not contain this level of detail.

6               We acknowledge continued reporting of fatal  
7       outcomes with TIRF medicines. We believe there is  
8       stimulated reporting of deaths generated by REMS  
9       activities such as re-enrollment and surveys.  
10       Heightened public awareness of fentanyl overdoses  
11       may also be contributing to report of these and  
12       other opioid products.

13              Overall, we have shown that many fatal cases  
14       reported to FAERS lack important details such as  
15       cause of death, concomitant diseases and  
16       medications, opioid tolerance status, and reasons  
17       for TIRF use for assessment. It is important to  
18       note a causal relationship between a product and  
19       event is not required for reporting to the FDA  
20       MedWatch program or product manufacturer. Overall,  
21       no definitive conclusions can be made from these  
22       FAERS data.

1           So FDA directed the sponsors to develop new  
2 studies. Remember, this was to understand the  
3 risks associated with prescribing TIRF medicines to  
4 opioid non-tolerant patients. And to study risk of  
5 overdose in opioid non-tolerant patients, we first  
6 needed to confirm that the study was identifying  
7 opioid tolerance accurately.

8           The FDA directed the sponsors to conduct an  
9 opioid-tolerance algorithm validation study. In  
10 June 2018, the sponsors submitted a study protocol  
11 to validate the claims-based algorithm with medical  
12 records. The study includes 127 patients in Henry  
13 Ford Health System, a closed healthcare system in  
14 Detroit, Michigan, and it includes data on  
15 inpatient use and outpatient dispensings. The  
16 protocol is undergoing review by FDA and the local  
17 institutional review board.

18           I want to run down some limitations of  
19 estimating the prevalence of opioid tolerance via  
20 claims algorithms. First, the algorithm may  
21 systematically miss sources of opioid therapy.  
22 Separate from that, the calculated average daily

1       dose consumed may be inaccurate.

2               As far as efforts to address these  
3       limitations, there are two validation studies, the  
4       sponsor study that's in development and our guest  
5       speaker, Dr. Molly Jeffery, will present her work,  
6       which is a collaboration between Yale, Mayo Clinic,  
7       and FDA to validate the algorithm using claims and  
8       medical record data from Optum. Another limitation  
9       is the study estimating opioid tolerance prevalence  
10      lacked data from the pre-REMS period, so it did not  
11      evaluate change. To begin to address this, our  
12      guest speaker, Dr. Will Fleischmann's presentation  
13      will include pre- and post-REMS data from his  
14      analysis of Medicare data.

15              The next question we seek to answer is to  
16      evaluate the overdose risk among patients starting  
17      TIRF medicines who are opioid non-tolerant versus  
18      opioid tolerant. In November 2016, given the  
19      opioid tolerance was estimated at 58 percent, FDA  
20      asked the sponsors to study adverse outcomes in  
21      opioid, non-tolerant patients.

22              FDA and the sponsors entered into a dialogue

1 on how best to conduct this study. In December  
2 2017, FDA asked the sponsors to submit a protocol  
3 for a study of the risk of fatal and non-fatal  
4 opioid overdoses among patients who are starting  
5 TIRF medicines by opioid tolerance status. When  
6 studying overdoses, particularly for potent opioids  
7 like fentanyl, it is vital to include cause of  
8 death data to count overdoses that are rapidly  
9 fatal.

10 The overdose study development status as of  
11 July 2018 is the sponsors are developing the study  
12 protocol in parallel with validating the opioid  
13 tolerance algorithm. The sponsors have submitted a  
14 feasibility assessment identifying 4 healthcare  
15 databases, each linked to cause-of-death data.  
16 They also submitted preliminary count data to help  
17 estimate the sample size needed from one database  
18 so far, and counts are expected from the other  
19 three.

20 Here are the 4 healthcare databases  
21 identified. Together, they are expected to provide  
22 about 3,100 opioid non-tolerant TIRF initiators and

1     about the same number who are opioid tolerant. It  
2     is important to have a sample size large enough to  
3     compare overdose incidence after adjusting for  
4     concomitant medications and other confounders. We  
5     expect submission of the quantitative feasibility  
6     data, but it may be that the surest way to accrue  
7     enough patients is to use all 4 databases in the  
8     overdose study.

9             These are key challenges FDA has identified  
10    to developing the study of overdose risk by opioid  
11    tolerance status, and in the second column are  
12    potential ways the protocol could address these  
13    challenges. One challenge is the extent of  
14    misclassification of exposure from the opioid  
15    tolerance algorithm. If the opioid tolerance  
16    algorithm is shown to have poor validity, it may be  
17    necessary to use medical record data.

18            Another challenge is the extent of  
19    misclassification of overdoses identified from  
20    medical claims codes. A sensitivity analysis that  
21    examines the risk of fatal overdose may address  
22    this if feasible. Potential confounding by

1 concomitant medications could be addressed with  
2 multivariable adjustment methods. And the count  
3 data may show the actual sample size is small, so  
4 the protocol should assess the expected statistical  
5 precision in for databases.

6 Here are the conclusions. They are 58  
7 percent of patients who start a TIRF medicine are  
8 opioid tolerant as determined by a claims-based  
9 algorithm; 42 percent are non-tolerant. This is  
10 concerning, and FDA sought more information. FAERS  
11 reports lack the information we needed for  
12 assessment for opioid non-tolerance and deaths, so  
13 no definitive conclusions can be made about these  
14 cases.

15 The FDA directed the sponsors to conduct  
16 epidemiologic studies. The validation study for  
17 the opioid tolerance algorithm has a protocol  
18 submitted and under review. We still need  
19 information about the overdose risk in opioid  
20 non-tolerant patients' prescribed TIRF medicines  
21 and are expecting a protocol at the end of  
22 September 2018.

1           Now, I will present the data for objective  
2       2, which is about preventing inappropriate  
3       conversion between TIRF medicines. Objective 2 has  
4       less material than objective 2. It has the  
5       sponsor's submission, which is a persistency  
6       analysis of TIRF utilization and conclusions from  
7       our review. The sponsor submitted preliminary data  
8       requested by FDA as we wanted to first know how  
9       many patients are at risk of inappropriate  
10      conversion; in other words, change their TIRF  
11      therapy.

12           This question is preliminary to evaluation  
13      of the REMS effectiveness at preventing  
14      inappropriate TIRF medicine conversions. The next  
15      step to evaluate the prevention of inappropriate  
16      TIRF medicine conversions has not been done.

17           I'm going to skip the next couple of slides  
18      because the persistency analysis was covered by  
19      Dr. Stemhagen, so I'll go on to conclusions from  
20      FDA review. Switching TIRF therapy occurred in  
21      20 percent of patients who filled 2 or more  
22      prescriptions over 12 to 42 months during 2012 to

1       2015. This is a general estimate of the population  
2       at risk for inappropriate conversions. The  
3       limitations of the study are that results are based  
4       on medicines dispensed, and it's unclear if they  
5       were consumed. Also, the results may not  
6       generalize to patients today as data were collected  
7       3 to 6 years ago.

8               The next step is for the sponsors to  
9       estimate the prevalence of inappropriate  
10      conversions and its trend over time. It is  
11      important to include TIRF medicine dosing  
12      instructions and other clinical details, and they  
13      may investigate patient outcomes after switching.  
14      FDA looks forward to reviewing the protocol.

15             Now I will present the data for objective 3,  
16      preventing accidental exposure to children and  
17      others for whom it was not prescribed. We have the  
18      sponsor's submission of calls to poison centers of  
19      the TIRF medicines in aggregate and spontaneous  
20      adverse event reports, which I will not present  
21      because the FDA-generated analyses produced greater  
22      detail on accidental exposures.



1           These are our analyses of FAERS and of  
2       poison center calls from the National Poison Data  
3       System, which enabled us to review the specific  
4       TIRF medicines involved in poison center calls,  
5       also the sponsor's new studies in development  
6       because FDA has asked for additional studies of  
7       accidental poisonings in children and conclusions  
8       from FDA's review.

9           Starting with the sponsor's submission, from  
10      the sponsor's submission, I will present adverse  
11      event rates per U.S. population and per  
12      prescriptions dispensed. The value of showing both  
13      kinds of rates is that each has unique strengths  
14      and limitations for evaluating adverse events  
15      associated with TIRF medicines. For the population  
16      adjusted rate, the strength is that it reflects the  
17      scope of the adverse event burden, especially  
18      relative to opioid comparators.

19           The limitations are that our data sources do  
20      not capture all adverse events, so cannot measure  
21      incidence. Also, as TIRF utilization declines, we  
22      would expect to see a decline in the population

1 adjusted rate. For the prescription adjusted rate,  
2 the strength is that it reflects the potential for  
3 harm from prescribing a TIRF medicine. Its  
4 limitation is, in this situation with utilization  
5 that is low and in decline, the prescription  
6 adjusted rate and its trend are potentially less  
7 reliable.

8 Using the poison center data, there was a  
9 pre- to post-REMS decrease in the mean population  
10 adjusted rate of accidental exposure involving any  
11 TIRF medicine, which is the first estimate on the  
12 left. There were few calls involving TIRF medicine  
13 exposure as you can see from the wide confidence  
14 interval. Decreases in the rates of accidental  
15 exposure calls were also observed across the  
16 comparator opioids during the same period.

17 These are the results for all accidental  
18 exposure calls, and the results for pediatric  
19 accidental exposure calls are almost identical. As  
20 for prescription adjusted rates of accidental  
21 exposure calls, the results were consistent with  
22 the results for population adjusted rates. There

1        were pre- to post-REMS decreases in the rate of  
2        accidental exposure calls involving TIRF medicines  
3        and involving comparators. Note, the wide  
4        confidence interval indicates an unstable estimate  
5        for TIRF medicines.

6                Given the challenges of studying this rare  
7        outcome, FDA looked into the FAERS data to  
8        characterize the adverse events associated with  
9        accidental exposures that have been reported to the  
10       FDA. This slide lists the adverse events by system  
11       organ class shown in bold. We found 13 cases in  
12       adults and children. Of these, 5 cases reported  
13       serious outcomes, 3 in children and 2 in adults,  
14       all of which were reported prior to the  
15       implementation of the TIRF REMS. None of these  
16       resulted in death.

17                The adverse events reported in children are  
18        boxed, and they all involved a TIRF lozenge. The  
19        remaining 8 cases were non-serious and reported in  
20        adults. Seven of the 8 cases reported Subsys  
21        exposure, and the adverse events reported were  
22        related to its spray formulation.

1           FDA was concerned about accidental  
2 exposures, though rare, involving the lozenge, so  
3 we searched for the specific TIRF medicines  
4 involved in accidental exposures in young children  
5 through our access to all U.S. poison center calls  
6 via the National Poison Data System. We found no  
7 deaths or major medical outcomes. There were  
8 5 calls in 2 years pre-REMS, and 5 calls in 5 years  
9 post-REMS. Most calls did involve Actiq or generic  
10 fentanyl citrate lozenge, except one for sepsis  
11 exposure.

12           FDA also directed the sponsors to undertake  
13 new studies of accidental poisonings in children.  
14 The reason for this objective is if a child gets  
15 hold of a TIRF medicine, the potency and dosage  
16 forms pose a risk of fatal respiratory depression.  
17 Our studies of poison center calls and adverse  
18 event reports yielded no fatal accidental exposures  
19 in children.

20           However, related research has shown that  
21 fatal overdoses generally are under-ascertained by  
22 poison centers and to an extent that varies by

1       toxin. So in March 2017, FDA requested that the  
2       sponsors complement their poison center  
3       surveillance data with data from medical records,  
4       emergency department and other healthcare claims,  
5       and death certificates to capture the childhood  
6       poisonings with severe outcomes.

7               The sponsors have started studies of  
8       accidental poisonings in children zero to 6 years  
9       old using healthcare claims linked to medical  
10      records and data mined from the literal text of  
11      death certificates. They also assess the  
12      feasibility of using the nationwide emergency  
13      department sample.

14             The conclusions for the review of data for  
15      objective 3 are accidental childhood poisoning  
16      remains a safety concern. Incomplete ascertainment  
17      of cases is possible. Poison center data suggests  
18      a post-REMS in rates but may miss the most severe  
19      cases. We found a small number of accidental  
20      exposures in adults and children reported to FAERS.

21             So FDA has recommended enhancing the rigor  
22      of surveillance to achieve as complete an

1       ascertainment of cases as possible. Even then, the  
2       outcome may be too rare to estimate change over  
3       time. We will see. The sponsors are undertaking  
4       two new studies. One uses death certificate  
5       literal text and is under FDA review. The other  
6       uses medical records with claims linkage, and FDA  
7       is expecting submission of the protocol.

8               Now I will present the epidemiologic and  
9       surveillance data to evaluate the goals of the TIRF  
10      REMS, which are to mitigate the risk of misuse,  
11      abuse, addiction, overdose, and serious  
12      complications due to medication errors.

13             The epidemiologic and surveillance data to  
14      evaluate the goals come from many sources, the  
15      sponsor's submission, which Dr. Richard Dart  
16      presented earlier, and I will show some highlights  
17      again of the RADARS poison center program and the  
18      RADARS treatment center program with results for  
19      TIRF medicines in aggregate.

20             There are FDA-generated analyses of the  
21      RADARS treatment center program where we looked at  
22      specific TIRF medicines, AAPCC National Poison Data

1 System and Inflexxion NAVIPPRO treatment center  
2 data, and also a social media search, and the  
3 conclusions from FDA's review.

4 This table shows outcome by data source.  
5 Outcomes are in the first column. The next  
6 2 columns are the sponsor's submission which  
7 analyzed TIRF medicines in aggregate. The next  
8 4 columns are FDA generated analyses of specific  
9 TIRF medicines. The open squares denote results  
10 that are included in the background package but not  
11 in the presentation because they do not add further  
12 information. The social media search was not in  
13 the background package but we thought it was  
14 important to summarize it here.

15 Now I will present data from the sponsor's  
16 submission. First, I will highlight and compare  
17 several important design issues in the RADARS  
18 treatment center program and poison center program.  
19 The respective populations are U.S. adults starting  
20 an opioid addiction treatment program and people  
21 calling participating U.S. poison control centers  
22 to seek medical advice for a drug exposure.

1           The data collection for the treatment center  
2 program is respondents fill in a survey to select  
3 the specific brand and generic prescription drugs  
4 they abused in the past 30 days. Data collection  
5 for the poison center program is by trained  
6 personnel who asked the caller for details on the  
7 exposure, reason, and product name from the  
8 container.

9           Data on illicit fentanyl is collected by the  
10 treatment center program by a survey item before  
11 the TIRF medicines as well as after. The poison  
12 center program data entry differentiates TIRF  
13 medicines from illicit fentanyl or simply fentanyl.  
14 Treatment center data showed a pre- to post-REMS  
15 decline in the mean population adjusted rate of  
16 abuse of TIRF medicines.

17           Most comparator opioids also showed a pre-  
18 to post-REMS decline in the mean population  
19 adjusted abuse rate. There was basically no change  
20 in the mean prescription adjusted rate of TIRF  
21 medicine abuse pre- to post-REMS. In contrast,  
22 most comparators exhibited a decline in the mean



1 prescription adjusted rate of abuse during the same  
2 period.

3 In poison center data, there was a  
4 suggestive increase in the mean population adjusted  
5 rate of calls involving TIRF medicine abuse. This  
6 estimate was based on few calls, so the confidence  
7 interval is wide. In contrast, most comparator  
8 opioids showed a pre- to post-REMS decline or no  
9 change in the mean population adjusted abuse rate.

10 The increase in the mean prescription  
11 adjusted rate of calls involving TIRF medicine  
12 abuse was larger, but the confidence interval was  
13 still wide because there were few cases. In  
14 contrast, most comparator opioids showed a pre- to  
15 post-REMS decline or no change in the mean  
16 prescription adjusted abuse rate.

17 Looking at the other outcomes in poison  
18 center data, the means for population adjusted  
19 rates of calls involving TIRF medicine exposure due  
20 to misuse or unintentional therapeutic error  
21 decreased pre- to post-REMS as did calls resulting  
22 in ED visits or hospitalizations. These changes in

1 the means were all similar to what was observed  
2 among comparators. There was a suggestive increase  
3 in the main population adjusted rate of calls for  
4 TIRF exposure resulting in major medical outcomes  
5 and deaths based on few calls.

6 Now, I'm showing the change in the mean  
7 prescription adjusted rates of these outcomes.  
8 There were suggestive increases in the main  
9 prescription adjusted rates of TIRF calls due to  
10 misuse and unintentional therapeutic error, calls  
11 resulting in emergency department visits or  
12 hospitalizations, and there was an increase in the  
13 mean prescription adjusted rate of major medical  
14 outcomes and deaths resulting from TIRF medicine  
15 exposure. The confidence interval is wide because  
16 there were a few calls.

17 I will now show results of FDA-generated  
18 analyses. FDA generated its own analyses of  
19 treatment center and poison center data to enable  
20 review of TIRF medicines results in aggregate and  
21 byproduct. Prior data from the 60-month REMS  
22 assessment suggested pre- to post-REMS increases in

1 select adverse event rates involving TIRF medicines  
2 in aggregate. And we wanted to see if broad  
3 patterns in the product-specific analyses were  
4 consistent with the TIRF aggregate results, or if  
5 there were discrepancies with the adverse event  
6 rates increasing for some TIRF medicines but not  
7 for others. Furthermore, some TIRF medicines were  
8 not marketed pre-REMS, so we wanted to make  
9 comparisons among products that were marketed pre  
10 and post.

11 In the product-specific data, it was  
12 feasible to estimate increases for Actiq generic  
13 lozenge and Fentora pre- to post-REMS in the  
14 prescription adjusted rate of emergency department  
15 visits and hospitalizations found in poison center  
16 data, consistent with the increase in the  
17 prescription adjusted rate of emergency department  
18 visits, hospitalizations, for all TIRF medicines,  
19 which I showed on a previous slide. Abstral,  
20 Lazanda, Onsolis, and Subsys could not be analyzed  
21 due to sparse data.

22 Now that I have shown you the comparison of

1 means pre- versus post-REMS, I want to discuss some  
2 limitations, the comparison of means for REMS  
3 evaluation. As you know, during the pre-REMS and  
4 post-REMS periods, there were trends in TIRF  
5 medicine prescribing, opioid prescribing, and  
6 opioid abuse and overdose, all of which are  
7 potential influences of trends in TIRF abuse. But  
8 a mean is a single summary measure, and therefore  
9 it can lose information if TIRF abuse is changing  
10 during the pre-REMS and post-REMS periods.

11 Let's look at the trends in recent abuse of  
12 TIRF medicines during the pre- and post-REMS  
13 periods. This is a plot of cases of self-reported  
14 recent abuse of any TIRF medicine in the RADARS  
15 treatment center program by calendar quarter.  
16 Cases of abuse declined throughout the pre-REMS  
17 period. This decline stopped in the post-REMS  
18 period. Cases of abuse hovered around 40 to 57 per  
19 quarter, and in the past year, cases are declining.

20 We also noticed that some individual  
21 products had patterns that went up and down even  
22 more during the post-REMS period, and this is part

1 of what we were talking to the RADARS team about,  
2 as we talked about before the break, and I will get  
3 into that later.

4 This is a plot of the population adjusted  
5 abuse rates of TIRF medicines, the solid black line  
6 with the red arrow pointing to it and opioid  
7 comparators. The rate uses the cases from the  
8 previous slide, and as you can see, the scope of  
9 abuse of TIRFs was low compared to other opioids  
10 during the pre- and post-REMS periods. Notice the  
11 line above the TIRF rate is the unknown fentanyl  
12 abuse rate, which increased during the post-REMS  
13 period.

14 When we look at the plot of prescription  
15 adjusted abuse rates, the TIRF abuse rate was  
16 higher than most comparator opioids. TIRFs are the  
17 solid black line with the arrow pointing to it.  
18 The prescription adjusted TIRF abuse rate increased  
19 throughout most of the post-REMS period since, as  
20 you recall, cases of abuse were fairly constant and  
21 prescriptions declined. So FDA looked into the  
22 prescription adjusted abuse rates of specific TIRF

1 medicines and no one product explained the  
2 increase.

3 We went back to our contractors from RADARS  
4 to investigate further this increasing rate we were  
5 seeing, and these discussions led to some new  
6 findings from the RADARS treatment center program.  
7 These results came in very recently, as we've said  
8 before, which is why they're not in the background  
9 package. FDA followed up on reasons for abuse  
10 patterns observed, and RADARS examined their data.  
11 They found no clustering by place or time, but they  
12 did show response patterns suggesting survey  
13 respondent careless reporting that substantially  
14 affects the results of low-volume products.

15 This is part of ongoing FDA-funded research  
16 on the quality of reporting of abuse of specific  
17 products. When using this method, people complete  
18 a survey about what they've abused in the past 30  
19 days when they've started treatment for abusing  
20 opioids. If there's careless reporting by survey  
21 respondents, this can more substantially affect the  
22 results of any low-volume products, and TIRFs are

1 just one example.

2 Here is a summary of the methods used to  
3 identify response patterns suggesting careless  
4 reporting, basically checking off items  
5 indiscriminately. One method is the outlier  
6 analysis to identify respondents who selected a  
7 large number of items. Another method is the  
8 modified long-string analysis to identify  
9 respondents who selected a large number of items in  
10 a row. This has a high degree of overlap with the  
11 outlier analysis, so I will not discuss it further.

12 To identify careless reporting with the  
13 outlier analysis, the RADARS team plotted the  
14 number of products reported on each survey with one  
15 or more drugs reported in 2017. Most of the  
16 surveys reported recent abuse of a few products,  
17 but there was a long tail of the distribution, as  
18 you can see in the oval.

19 The upper 2.5 percent of surveys in the  
20 distribution reported recent abuse of 25 or more  
21 specific products in the past 30 days. Among  
22 surveys that reported abuse of a TIRF medicine, the

1 median number of products reported is 22. That  
2 means that nearly half of reports of TIRF medicine  
3 abuse may be due to careless reporting.

4 These late-breaking findings mean a  
5 substantial proportion of treatment center program  
6 reports of TIRF medicine abuse may be unreliable.  
7 RADARS will update the drug abuse surveillance  
8 results, and FDA expects the small number of cases  
9 will be even smaller.

10 Regarding the data sources for abuse, there  
11 are other important limitations to point out. For  
12 treatment centers, findings may not generalize to  
13 all people who abuse drugs or who seek treatment.  
14 Also, poison centers have the limitation of under  
15 ascertainment of exposures with severe outcomes  
16 such as death, and this under ascertainment of  
17 exposures may vary over time and by toxin.

18 Finally, I want to summarize a social media  
19 search that we did of each TIRF medicine during the  
20 pre- and post-REMS periods to see if we were  
21 missing any themes that might come out in social  
22 media posts, whether there were mentions of



1 counterfeit TIRF medicines being abused and  
2 qualitative changes in the discussion over time.  
3 We found postings related to the abuse of each TIRF  
4 medicine, but we found no mentions of counterfeit  
5 TIRF medicines or qualitative trends in the  
6 discussion.

7 The conclusion from FDA's review are that  
8 we're concerned about increases in rates of poison  
9 center calls of abusive TIRF medicines, although  
10 based on few events, and major medical outcomes and  
11 deaths attributed to TIRF medicine exposure, also  
12 few events. There were relatively few reports of  
13 abuse and treatment center data, and late-breaking  
14 findings from RADARS suggest careless reporting by  
15 respondents affected the TIRF medicines results.  
16 FDA is expecting the updated results.

17 We observed few events but suggestive  
18 increases in prescription adjusted rates of poison  
19 center calls due to unintentional therapeutic  
20 error, misuse of TIRF medicines, and exposures to  
21 TIRF medicines resulting in ED visits and  
22 hospitalizations. Thus, these results are

1       difficult to interpret.

2               We have completed the review of  
3       epidemiologic and surveillance data related to the  
4       REMS goals and objectives 1 through 3. Here are  
5       the summary conclusions for each objective. For  
6       objective 1, ensuring use in appropriate patients,  
7       50 percent of patients who are starting TIRFs are  
8       opioid tolerant. Cross out the "non." I'm sorry.  
9       That was an error. FDA's concerned and has  
10      directed the sponsors to undertake further studies  
11      to understand associated outcomes and algorithm  
12      validity. FAERS data are inconclusive.

13              For objective 2, preventing inappropriate  
14      conversions, 20 percent of patients with 2 or more  
15      TIRF dispensings changed regimen and are at risk  
16      for inappropriate conversions. FDA looks forward  
17      to reviewing a protocol for a study of  
18      inappropriate conversions.

19              For objective 3, preventing accidental  
20      exposures, poison center call rates declined. To  
21      capture the most severe cases, sponsors are  
22      undertaking additional studies of accidental

1 childhood poisoning. And for the goals of  
2 mitigating abuse, misuse, overdose, and other  
3 adverse events, suggestive increases in rates of  
4 select adverse events were observed, although based  
5 on few events.

6 I would like to acknowledge the FDA  
7 contracts with RADARS AAPCC, and the epidemiologic  
8 surveillance data review team.

9 **FDA Presentation - Doris Auth**

10 DR. AUTH: I just have a few slides on  
11 concluding remarks before we have some questions  
12 and break for lunch.

13 Early this morning, Dr. Kilgore presented a  
14 review of the regulatory history of the  
15 transmucosal immediate-release fentanyl products,  
16 which are potent, rapidly-acting, opioid  
17 analgesics. Because of the safety concerns she  
18 outlined, the TIRF REMS was required to address the  
19 potential for significant respiratory depression  
20 and death in patients who are not opioid tolerant  
21 and in individual, particularly in children, who  
22 may accidentally ingest these products, and the

1 potential for medication errors and adverse events  
2 associated with inappropriate conversion between  
3 TIRF products and the risks of abuse, misuse, and  
4 overdose.

5 The TIRF REMS was designed to address these  
6 risks with minimal burden on the healthcare  
7 delivery system and patient access through a  
8 mechanism to educate prescribers and pharmacists,  
9 counseling of patients on risks and safest  
10 practices, and ensuring that enrolled prescribers  
11 only prescribe to patients who have completed a  
12 patient provider agreement form.

13 The assessment findings over the 6 years of  
14 experience we've had with the TIRF REMS show that,  
15 in general, this REMS has been implemented and  
16 continues to operate as intended. Overall,  
17 utilization of TIRF products and enrollment in the  
18 TIRF REMS has been declining.

19 In general, as shown by the surveys of  
20 knowledge, knowledge of risks and safe-use  
21 practices are high for the majority of risk  
22 messages These and opioid on tolerant patients is

1       concerning, and the outcome measures have been  
2       challenging to obtain, also showing some results,  
3       some concerning findings.

4               We've outlined in our presentations, some  
5       REMS assessment gap. First, what is the impact of  
6       declining utilization and prescriber enrollment on  
7       appropriate patient access to these products? Why  
8       are prescribers and pharmacies not re-enrolling in  
9       the TIRF REMS. Why are prescribers and pharmacies  
10      not re-enrolling in the TIRF REMS? Is the opioid  
11      tolerance algorithm valid?

12             We also have some questions on the best  
13      methods for setting overdose events in non-opioid  
14      tolerant, first opioid-tolerant patients,  
15      accidental poisonings in children, and abuse and  
16      misuse data considering the recent RADARS findings  
17      that were presented this morning. Thank you.

18                             **Clarifying Questions**

19               DR. BATEMAN: Thank you.

20               So we have a few minutes for clarifying  
21      questions for the FDA. Please remember to state  
22      your name for the record before you speak. If you

1 can, please direct questions to a specific  
2 presenter. Dr. Higgins?

3 DR. HIGGINS: Jennifer Higgins. This  
4 question is for Dr. Auth. You mentioned that one  
5 potential reason for the decline in prescriber  
6 enrollment may be based on the burden to providers.  
7 Is there any evidence of that? That seems like an  
8 important facet that should be measured, and I'm  
9 wondering if there's any data on that at all or  
10 there are plans to collect.

11 DR. AUTH: I'm still back here. We do  
12 appreciate that the TRIG had conducted some  
13 outreach to prescribers and pharmacists, but we  
14 agree that we really didn't get any particularly  
15 useful information on that very issue. So they are  
16 going to be conducting further outreach with  
17 prescribers to get to the heart of why they're not  
18 enrolling.

19 DR. BATEMAN: Dr. Joniak-Grant?

20 DR. JONIAK-GRANT: I have two quick  
21 questions. One is for Dr. Auth in reference to  
22 slide 21 regarding the target knowledge rate of 80

1       percent. In your presentation, you said there  
2       really is no standard, but 80 percent is used in  
3       most cases. And I was wondering if this is used  
4       for all types of medications, or certain classes of  
5       drugs, or if there's particular risk; that  
6       80 percent is seen as not enough and how that's  
7       sort of decided, or is it just kind of thrown at  
8       the wall.

9               My second question will be for Dr. Radin in  
10       reference to slide 69 to 71, about the careless  
11       reporting. It seems like there's a cluster, if I  
12       understand correctly, of outliers that might be  
13       explained by careless reporting.

14              Is there any one or any way to track down  
15       one or two, at least, individuals and talk to them,  
16       and ask them about how they felt about -- to see if  
17       there are some things going on. I know I've worked  
18       with certain populations where you might think it  
19       was careless reporting, but it's not.

20              DR. RADIN: That is a good question, And to  
21       the best of my knowledge, that's not possible. But  
22       I am looking at -- I see Dr. Richard Dart is

1        nodding, that it's a confidential survey, so they  
2        don't have the names of people to follow up with  
3        them.

4                DR. AUTH: With respect to your first  
5        question about the target knowledge rate of 80  
6        percent, we had a public meeting on this way back  
7        in 2012, and we're hoping to have a guidance  
8        published soon on this.

9                We certainly appreciate if the sponsors,  
10       when they submit their survey methodology, have  
11       rationale for providing or targeting a knowledge  
12       rate that's either above or below the 80 percent.  
13       And I think even within ourselves, we've criticized  
14       ourselves that sometimes 80 percent is too high.

15               So there's always room, and that's why we  
16       say generally 80 percent, we recommend, but we can  
17       certainly understand why some particular  
18       stakeholders may not reach that knowledge rate and  
19       why some should be closer to 100 percent.

20               DR. BATEMAN: Dr. Katzman?

21               DR. KATZMAN: Thank you. This is a question  
22       for either Dr. Auth or Dr. Radin. I agree it's



1       concerning that the prescribing of these TIRF meds  
2       are dropping despite the prevalence of cancer going  
3       down. I'm wondering if you've looked at perhaps  
4       any geographic declines or rural declines in the  
5       prescribers or pharmacies that are writing for or  
6       using these medications that might put patients who  
7       have cancer at risk for being able to acquire these  
8       medications. That's my first question.

9               My second question is, for patients with  
10       cancer in moderate to severe pain who need these  
11       meds, when they go to a facility, do they know if  
12       the prescriber writes for the med. Many more  
13       patients nowadays are so savvy and are  
14       knowledgeable about their own health care. Thank  
15       you.

16              DR. AUTH: The first question about the  
17       geographic location of prescribers and pharmacies,  
18       the very first time that we reviewed the TIRF REMS  
19       assessment, we did ask for location, geographic  
20       location. I don't recall if it was just the first  
21       or the second assessment. And at that time, we  
22       didn't have many concerns, that there appeared to

1 be coverage throughout the country. However, you  
2 make a really good point, and that is something  
3 that we are interested in learning more about.

4 I'm not sure I'm the best person to answer  
5 the second question, though, about whether patients  
6 are aware of there being prescribed a TIRF  
7 medicine. I think that's what you were asking.

8 DR. RADIN: I don't have an answer for that  
9 either.

10 DR. KATZMAN: Excuse me. What I was asking  
11 is, is there a way for a patient to know whether  
12 the facility has any prescribers who are certified  
13 to write for a TIRF medication?

14 For instance, I come from University of New  
15 Mexico. It's the only safety net hospital. I'm  
16 not positive there are many physicians who are  
17 certified for writing for TIRF medications. Thank  
18 you

19 DR. AUTH: I don't know the answer to that  
20 question. I apologize.

21 DR. BATEMAN: Dr. Brown?

22 DR. BROWN: This is for Dr. Dart.

1           Dr. Dart, I've been listening to the  
2       presentations, and it seems to me that a lot of our  
3       analysis is predicated on the distribution of  
4       poison control center coverage in the United  
5       States. And repeatedly it's been said that there's  
6       90 percent coverage, and there was a very nice  
7       slide that -- and I'm wondering about that  
8       statement that there's 90 percent coverage of  
9       poison control in the United States.

10           How did you derive that?

11           DR. DART: Legally, each poison center has  
12       to be officially designated for a geographic area.  
13       For example, the state of Colorado would have to  
14       officially designate my center, Rocky Mountain, as  
15       the poison center for that area. So we take those  
16       populations and add them up. There's a total of 55  
17       poison centers in the United States. Fifty  
18       participate in RADARS, and that comes to 94 percent  
19       of the population that have official designations  
20       to cover those areas.

21           DR. BROWN: Rick, do you have any  
22       information about the likelihood that any

1 independent population in a state is going to  
2 actually have the availability of the use of a  
3 poison control center?

4 DR. DART: That's a good question. Each  
5 center has to have a toll free number available for  
6 them to call, and they have to show penetrance into  
7 each county inside the state. But I think one  
8 thing that you're getting at that that was said  
9 earlier, but we should perhaps repeat it, is this  
10 is spontaneous reporting.

11 A poison center is required to advertise and  
12 promote themselves inside their service area, but  
13 in general, I would say that -- I mean, we looked  
14 at this for various drugs. And basically we would  
15 see, in the case of deaths -- I've talked to talked  
16 to Margie [ph] about this before -- 5 to 10 percent  
17 of the deaths that are related would actually have  
18 contacted a poison center in the case of opioids.

19 DR. STAFFA: This is Judy Staffa. Can I  
20 just clarify one thing? I just want to make sure  
21 we differentiate. Technically, poison control data  
22 are not really spontaneous reporting data.

1 Spontaneous reporting data, as we've discussed them  
2 in these presentations, are what sponsors are  
3 required to report under law to FDA and what we  
4 often receive, direct reports from healthcare  
5 providers and patients.

6 Those are reported to us spontaneously, and  
7 we do not know how much they represented everything  
8 that happens out there. There are limitations to  
9 poison control center data, but they're not the  
10 same as the limitations to the spontaneous  
11 reporting data. People call poison control data  
12 because they need information or assistance. So  
13 it's a different animal, different limitations. I  
14 just want to make sure that's clear.

15 DR. AUATH: And I would also like to amend  
16 my answer to Dr. Katzman's question about whether a  
17 provider is available. I believe that that is  
18 something that can be obtained by calling the REMS  
19 center, and the TRIG can back me up on that. I  
20 don't know, however, if the patients are even aware  
21 the program exists.

22 DR. BATEMAN: Dr. Litman?

1 DR. LITMAN: Thanks.

2 Dr. Auth, I'm really interested about the  
3 difference between independent and chain  
4 drugstores. I think that could be an interesting  
5 sociological question. I don't even know anybody  
6 that gets their prescriptions at an independent.  
7 Could you be just more granular? What were the  
8 definitions there of what independent versus chain  
9 were?

10 DR. AUTH: I believe the independent,  
11 according to the TRIG -- and again, please clarify  
12 this if I'm incorrect -- included independent  
13 stores that were not chain retail pharmacy stores,  
14 and also included long-term care facilities. And  
15 I'm going to look to Igor Cerny in the audience to  
16 clarify this. I don't remember.

17 There were three categories, although we  
18 would think that the majority of these dispensing  
19 would be from the independent stores. I think the  
20 third one was mail order mail order.

21 DR. CERNY: Yes. It was mail order, and I  
22 believe it was a clinic associated with an

1 institution that is outpatient. But the relative  
2 proportions we didn't know. So I would defer to  
3 the TRIG on that.

4 DR. AUTH: We agree that it is a really  
5 interesting finding. In some cases, maybe it's a  
6 good thing that these independents are handling the  
7 majority because they're willing -- we know that  
8 these are expensive products, and they're willing  
9 to keep them on their shelves to take care of these  
10 patients.

11 DR. LITMAN: Well, not only that, but they  
12 may be more willing to participate with any kind of  
13 rider in the REMS program. And keeping their  
14 patients safe, they're sort of like neighborhood  
15 type patients as opposed to the chains that might  
16 be more -- well, I don't -- less.

17 DR. AUTH: Yes. We agree that it was a  
18 curious finding, that we're interested in learning  
19 a little more about that.

20 DR. BATEMAN: Okay. Last question before  
21 lunch. Dr. Meisel?

22 DR. MEISEL: It's always bad to be the

1 person last before lunch. Steve Meisel with  
2 Fairview, Minneapolis. I'm not exactly here who to  
3 address this question to, and TRIG could answer  
4 this as well. Every conclusion from both TRIG and  
5 from the FDA has been that the REMS is working as  
6 designed. Yet, virtually every data slide that  
7 we've been presented today from both FDA and TRIG  
8 has identified patients who are not opioid  
9 tolerant, has identified patients who don't have  
10 cancer, and patients who are under the age of 18  
11 who received this product.

12 How could the program be operating as  
13 designed if such a high level of noncompliance, if  
14 you will, goes along with that? I looked at the  
15 enrollment form, PPAF, and it's crystal clear,  
16 maybe not for peds [indiscernible], but for all the  
17 other topics, it's crystal clear.

18 Are doctors lying on the form? Why do we  
19 have this disconnect? And if we have a disconnect,  
20 how could we be concluding that the REMS program is  
21 operating and functioning as designed?

22 DR. AUTH: Just to go back to the



1 requirements of the REMS, there's an educational  
2 program for prescribers and pharmacists that they  
3 must take, and they have to enroll, and they have  
4 to go over the agreement form with their patients  
5 with certain attestations. And when the program  
6 was designed, again, it was designed with primarily  
7 an educational focus. And then the pharmacy  
8 component was to make sure that prescriptions were  
9 only being dispensed to prescribers who are  
10 enrolled.

11 I'd like to point out that there is no  
12 active intervention at the point of dispensing.  
13 There is no -- we don't make certain that the  
14 patients are opioid tolerant. There's not a form  
15 that you have to fill out that shows exactly what  
16 your patient was on before you're authorized to  
17 dispense a prescription. There's also no  
18 information about whether the patient has cancer  
19 pain or pain related to another source.

20 So when we say that it's operating as  
21 intended, we mean it's operating to ensure that  
22 prescribers and pharmacists are educated, and that

1       there is that check at the pharmacy that the  
2       prescriber has taken that education prior to  
3       dispensing the prescription.

4               DR. LITMAN: But the doctor has signed the  
5       PPAF form, and the PPAF form says my patient's got  
6       cancer, and they're opioid tolerant, and it defines  
7       all that sort of stuff. And somehow they get to  
8       the center and they get -- are they lying on that  
9       form or -- I mean, how does it get through that  
10      way? Maybe TRIG can answer.

11             DR. AUTH: The form is just I understand  
12      that patients should be -- I understand that the  
13      TIRF medicines are indicated for cancer patients  
14      with breakthrough pain. So again, they're not  
15      attesting that my patient has cancer and my patient  
16      is opioid tolerant.

17             DR. BATEMAN: Thank you.

18             We'll now break for lunch. We'll reconvene  
19      again in this room in 15 minutes at 12:45. Please  
20      take any personal belongings you may want with you  
21      at this time.

22             Committee members, please remember that

1       there should be no discussion of the meeting during  
2       lunch amongst yourselves, with the press, or with  
3       any members of the audience. Thank you.

4               (Whereupon, at 11:56 a.m., a lunch recess  
5       was taken.)

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1                   A F T E R N O O N   S E S S I O N

2                                   (12:44 p.m.)

3                   DR. BATEMAN:   We will now proceed with the  
4                   guest presentations, Dr. Jeffery.

5                               **Guest Presentation - Molly Jeffery**

6                   DR. JEFFERY:   Good afternoon, everyone. My  
7                   name is Molly Jeffery.   I am a research scientist  
8                   at the Mayo Clinic in Rochester, Minnesota, and I  
9                   serve as the scientific director of research and  
10                  emergency medicine at Mayo Clinic.   Thank you so  
11                  much for the opportunity to present this work  
12                  today.

13                  I'm going to be telling you about some work  
14                  that we've been doing conducted through the Yale  
15                  Mayo Clinic Joint Center for Excellence in  
16                  Regulatory Science and Innovation. We have a big  
17                  team of colleagues from OptumLabs, the Yale-Mayo  
18                  Clinic, CERSI, and the FDA.   This study was  
19                  supported by a grant from the FDA, from the CERSI.

20                  What we were doing with this study is  
21                  seeking to characterize the frequency of  
22                  potentially unsafe prescribing practices of various

1       opioids that are subject to REMS. In addition to  
2       TIRFs that we're discussing today, we were also  
3       looking at extended-release opioids subject to  
4       REMS. But in this presentation, I'm going to  
5       concentrate on the TIRFs, for your sake.

6               There have previously been two major studies  
7       using claims data to understand opioid tolerance in  
8       people who are taking extended-release opioids. So  
9       part of the aim of this study in Aim 1 was to use  
10      claims data to replicate those analyses and then  
11      also to add TIRFs to the analysis beyond what had  
12      previously been done.

13             These claims-based studies, as was brought  
14      up this morning, raised the question of whether  
15      there could be some missing data, data missing from  
16      claims that would be present if we were able to  
17      look in the EHR or some other source of information  
18      about patients. So in Aim 2, we use structured EHR  
19      data and data from notes to try to determine  
20      whether we can find any additional evidence of  
21      opioid tolerance beyond what was found in claims.

22             Our data source with the OptumLabs data

1       warehouse. In Aim 1, we use claims data, and it's  
2       primarily enrollment data and pharmacy claims. In  
3       Aim 2, we use EHR data from OptumLabs data  
4       warehouse, which includes all pair types. The  
5       claims include only commercially insured and  
6       Medicare Advantage beneficiaries. We have both, as  
7       I said, EHR data and notes.

8               In the structured data, we can see things  
9       like reports of hospitalization, prescriptions  
10      written. We could see lab tests and things like  
11      that. In the clinical notes, those are free text.  
12      So those could be anything, and we need to do some  
13      advanced textual analysis to understand what's in  
14      there.

15             The definition that we used for the opioids  
16      requiring prior tolerance are here. As I said, I  
17      am concentrating today on TIRFs, so that is boxed  
18      in, in orange. And throughout when I present  
19      anything with the TIRFs, it will be boxed in, in  
20      orange, like that. The definition of opioid  
21      tolerance we used was the same one you heard this  
22      morning. So prior to starting the TIRF, we needed

1 to 7 days of at least 30 milligrams of oxycodone  
2 equivalence in the 7 days leading up to the first  
3 TIRF.

4 I've provided the other four, so in the  
5 broader study that we've done, we looked at four  
6 different measures of the tolerance that are from  
7 the Marc Larochelle study, but we are not  
8 presenting those just due to time today. So in  
9 terms of the claims data, what did we find?

10 Our inclusion criteria were that we required  
11 6 months of continuous enrollment with both  
12 pharmacy and medical benefits, and it could be  
13 commercial or Medicare Advantage. We required  
14 evidence of an opioid-tolerant only prescription,  
15 so that's what we're calling these, OTOs. Between  
16 January 1, 2007 and the end of 2016, to be  
17 considered, we required that they had no prior OTO  
18 prescription in the previous 6 months, and we also  
19 required that they have no diagnosis for opioid  
20 poisoning or overdose in the prior 6 months.

21 To address the concern that was raised  
22 earlier today that if somebody was hospitalized, we

1       might not see the medications that led to them  
2       being opioid tolerant. We excluded anyone who had  
3       a hospitalization in the prior 30 days. And after  
4       those exclusions, we included over 150,000 episodes  
5       of people starting on opioid tolerant-only  
6       prescriptions. The fentanyl patch was by far the  
7       most common of those that we saw; it was about  
8       two-thirds. But we were able to identify 2400 TIRF  
9       episodes.

10               Throughout this, I will always be presenting  
11       the proportion that were tolerant. Here, you can  
12       see in orange the TIRFs versus the fentanyl patch,  
13       extended-release hydromorphone, extended-release  
14       oxycodone. In the commercial group, 61 percent; in  
15       the Medicare Advantage, 75 percent demonstrated  
16       primary tolerance, so that's the previous 7 days at  
17       least 30 milligrams of oxycodone equivalence when  
18       they started the TIRFs. In comparison, you can see  
19       that 84 or 85 percent of people starting  
20       extended-release oxycodone demonstrated tolerance.  
21       And on the low end in the fentanyl patch, about a  
22       quarter to a third demonstrated tolerance when they



1 started on the fentanyl patch.

2 We stratified this analysis by age group,  
3 and you can see that in the TIRF group, we had very  
4 similar rates of tolerance across the age groups  
5 except for the oldest group, those aged 75 and  
6 older where only 50 percent demonstrated tolerance.  
7 We saw a similar pattern in fentanyl and  
8 extended-release hydromorphone where the 75-plus  
9 was the lowest rate of tolerance seen.

10 We were also asked to provide some  
11 information about TIRF episodes by the strength of  
12 the initial prescription, so we've divided it out.  
13 As we heard this morning, it's very difficult to  
14 convert between the different TIRF products, so  
15 this is directional.

16 As you can see, 4 percent of the people  
17 starting on TIRFs had the 1000-plus microgram  
18 strength. And when you look on the right at the  
19 opioid tolerance by the strength of that initial  
20 episode, you do see somewhat higher rates of  
21 tolerance in the people getting the highest doses.  
22 But there remain 27 percent of people starting on

1 the 1000-plus micrograms who did not show evidence  
2 of tolerance.

3 In summary, of the claims analysis, we had  
4 more than 150,000 OTO episodes studied. We had  
5 2440 TIRF episodes. The highest rates of tolerance  
6 were extended-release oxycodone. But in the TIRF  
7 episodes, we saw similar to what the sponsors have  
8 presented, 61 percent of the commercially insured  
9 and then 75 percent of Medicare Advantage  
10 demonstrated tolerance when they started.

11 So in Aim 2, as I said, there's this  
12 question about when you look at the claims analysis  
13 and see these large proportions of people who did  
14 not seem to be opioid tolerant, whether we must be  
15 systematically missing something. And if we could  
16 look at their electronic health record data, could  
17 we find some other evidence that the person  
18 actually was opioid tolerant?

19 So that's what we did in Aim 2. We used EHR  
20 data and notes data. The EHR data that we used is  
21 derived from dozens of healthcare provider  
22 organizations, 700 hospitals, and 7500 clinics. It

1 includes all insurance types, including people who  
2 are uninsured. But there's one thing to understand  
3 about EHR analysis if you are used to doing claims  
4 analysis, and that's there is no equivalent to the  
5 claims idea of continuous enrollment.

6 So when somebody has continuous insurance  
7 enrollment, we know that for that entire period,  
8 they're at risk for being observed to have some  
9 kind of healthcare use, and that if it a major,  
10 enough type of healthcare use, you will see a claim  
11 for it.

12 By contrast in the EHR, there is no such  
13 thing. If we don't see somebody having any  
14 interactions in the EHR, that could be because they  
15 haven't had any health care, but it could also be  
16 because they're receiving healthcare from outside  
17 the system. And there's no way to tell which one  
18 is the case, so we just need to keep that in mind.

19 But the balancing piece of that is that when  
20 we do have EHR data, it's incredibly rich. So as I  
21 said, we can see office visits, we can see  
22 consultation reports, we see pathology, labs,

1       nursing, all kinds of information. And in a subset  
2       of these patients, in addition to their structured  
3       data, we also have notes data.

4               In this portion of the study, we identified  
5       our sample by starting with our claims sample, our  
6       150,000 episodes in claims, and looking for the  
7       subset of those people who had any EHR activity  
8       within 183 days of starting their opioid  
9       tolerant-only opioid. The approach here is to  
10      compare the evidence of tolerance that we find in  
11      the claims data to evidence of tolerance that we  
12      see in the EHR.

13             This group comprised 20,000 OTO episodes  
14      that matched. In addition, we had more than 45,000  
15      episodes where we had notes for the person. So  
16      regardless of whether we actually could match them  
17      to the claims data, we could still use the text in  
18      their notes to understand and process using the  
19      natural language processing.

20             We did not, unfortunately, have enough TIRF  
21      episodes to present those separately, so they will  
22      be included in with all of the other drugs. But it

1 is worth noting that we did see a similar  
2 distribution of the proportion of episodes that  
3 were due to each drug, so at least in that way,  
4 there is no systematic difference between the two  
5 groups.

6 If you think about what we're trying to do  
7 in this Aim, think about it as a 2-by-2 table. So  
8 you have was there evidence of tolerance in the  
9 claim; yes or no? That's across the top. And then  
10 was there evidence of tolerance in the structured  
11 EHR data; yes or no? And the key box is the upper  
12 right. That's where we have no evidence in claims,  
13 that they were tolerant, but we did find evidence  
14 in the structured EHR data to suggest that they  
15 were opioid tolerant. And when we did that  
16 analysis, we had very limited additional  
17 information added by the structure at EHR data.

18 The second half of Aim 2 was the textual  
19 analysis of notes. We used machine intelligence  
20 called natural language processing to summarize all  
21 of the notes into topics. Within those topics, we  
22 also identified hundreds of important terms,

1 including by working with a technical expert panel  
2 of physicians and other experts to identify words  
3 that might suggest that the person was opioid  
4 tolerant; that they were taking opioids; that they  
5 had opioid misuse; or that they had some other  
6 reason why a physician, rightly or wrongly, might  
7 have prescribed an OTO despite no evidence of  
8 tolerance.

9           When we tested whether any of these topics  
10 or terms differentiated between people who did and  
11 did not have evidence of tolerance in our claims  
12 data, I don't have time to present the full  
13 results. But the high-level result is that there  
14 were no terms and no topics that were associated  
15 with missing evidence of tolerance in claims data.

16           In summary, studies using claims data have  
17 found substantial numbers of people receiving  
18 prescriptions for opioids that require tolerance in  
19 order to be used safely, and those patients did not  
20 in fact have evidence of tolerance. When we add  
21 EHR data either from structured fields or from  
22 using NLP on patient notes, we got a minimal amount

1 of additional evidence of tolerance.

2 So based on this exploration, we believe  
3 that the results of our end of previous claims  
4 analysis are largely accurate. But one thing to  
5 note is that we did not evaluate the implications  
6 of this potentially unsafe prescribing or whether  
7 there was any harm as a result of these  
8 prescriptions. Thank you.

9 DR. BATEMAN: The next presentation is going  
10 to be by Dr. Fleischman, who's joining by phone.

11 Dr. Fleischman, you can begin.

12 DR. FLEISCHMAN: Thanks. And can you  
13 confirm you can hear me okay.

14 DR. BATEMAN: Can you speak a little bit  
15 louder please?

16 DR. FLEISCHMAN: Sure. Can you hear me now?

17 DR. BATEMAN: I think that's better.

18 **Guest Presentation - William Fleischman**

19 DR. FLEISCHMAN: Good afternoon. My name is  
20 Will Fleischman. I'm an emergency physician, and  
21 I'm a medical officer at Center for Program  
22 Integrity at CMS. Just for some background -- and

1 I don't have any financial conflicts of interest to  
2 declare.

3 For some background, CMS is obviously very  
4 interested in this topic. We have worked for  
5 awhile to try to mitigate the harm of opioids for  
6 our beneficiary, and this program was a specific  
7 interest of ours because we wanted to see how a  
8 restricted prescriber in a program such as this  
9 [indiscernible], which is why we undertook this  
10 study.

11 You can go to the next slide, which are  
12 research questions. This is very straightforward.  
13 We wanted to know whether TIRF REMS decreased  
14 overall TIRF prescribing. We wanted to see whether  
15 it would decrease off-label prescribing or  
16 prescribing for patients without cancer. And we  
17 wanted to see whether the program decreased  
18 prescribing for patients who are not tolerant to  
19 opioids.

20 We asked some secondary questions, which  
21 were whether there were any differences by brand,  
22 by age group; whether the program affected the



1        number of prescribers differently than it affected  
2        the number of prescriptions; and the actual  
3        prescribing, whether it affected patients with and  
4        without cancer differently.

5                The next slide talks about more of the  
6        method. We used only Part D prescription claims,  
7        and we initially included -- the larger data  
8        included all Part D prescription claims for opioids  
9        from 2010 through 2014, so [indiscernible]. Some  
10       of the questions, we excluded prescription claims  
11       for Abstral, Lazanda, and Onsolis because these  
12       already had some form of REMS prior to 2012, and we  
13       wanted to isolate only the prescriptions that did  
14       not have an active REMS so we could see what the  
15       effect was of REMS implementation. We also  
16       excluded IV injectable fentanyl.

17               Next slide, please. In defining cancer, the  
18       primary way we defined cancer was that the patient  
19       did not have a cancer diagnosis during the  
20       prescription claim year. As a sensitivity  
21       analysis, we also used a broader cancer definition,  
22       where we defined it as the patient or beneficiary

1 not having a cancer diagnosis during the entire  
2 study period, so the entire 5 years. And we used  
3 HCC diagnoses switches, which are defined as yes/no  
4 switches that cover all claims and all visits for  
5 each year and each beneficiary. And Medicare  
6 defines these HCC risk switches. So we used the  
7 4 HCC switches, so to speak, that cover all cancer  
8 diagnoses.

9 Defining opioid tolerance has been discussed  
10 previously, and I know [indiscernible] how  
11 tolerance was defined. Our numbers might be  
12 [indiscernible] than the ones that have been shown  
13 up to this point because our definition was a bit  
14 more narrow. We looked at 7 to 14, 30, 60, and 90-  
15 day period prior to the first TIRF prescription,  
16 and non-tolerance was defined as if the patient had  
17 low tolerance thresholds [indiscernible].

18 If there was tolerance in any of these ALL  
19 look-back periods, then the patient was considered  
20 a tolerant patient. blue on that period. It's a  
21 very broad definition of tolerance, and we did this  
22 intentionally so our numbers would be conservative

1 and reliable.

2 Next slide, please. We did interrupted time  
3 series analysis, descriptive analysis as well. And  
4 the key feature for when you're doing a  
5 before/after kind of analysis, the key benefit of  
6 this [indiscernible], all the confounders that you  
7 can control, because you're having the  
8 pre-intervention period are as part of the  
9 calculation basically adjust and control for  
10 anything that didn't happen simultaneously with the  
11 REMS implementation.

12 For example, as I was thinking, the previous  
13 presentations were talking about the limitation of  
14 not harboring hospitalization data, it is certainly  
15 a limitation here, too. But that itself should not  
16 change REMS implementation, meaning there shouldn't  
17 be a higher percentage of people who suddenly  
18 gained tolerance during hospitalizations after REMS  
19 implementations. So that's a benefit of this time  
20 series approach.

21 We adjusted for the general happenings in  
22 the U.S. where people were getting more aware of

1 the opioid epidemic and the awareness and the drive  
2 to improve prescribing. So that could decrease, of  
3 course, prescribing on a phone without limitation,  
4 which is why all opioid prescriptions as a control.

5 We also did sensitivity analysis excluding  
6 buprenorphine in these cold prep medicines for  
7 disease curves, especially buprenorphine, people  
8 are transitioning from being addicted to going on  
9 MAT [ph], that could map an actual drop in opioid  
10 prescriptions. And we adjusted the time series  
11 analysis for autocorrelation, seasonal variation,  
12 and days in the month.

13 Next slide, please. Just in descriptive  
14 results, you can see we have 99,000 prescription  
15 claims in that 5-year period for TIRF medications,  
16 and this includes the Abstral, Onsolis, and  
17 Lazanda, given by 8600 clinicians for about 10,500  
18 patients. The average age was 56 years, so this  
19 indicates that most prescriptions -- 79 percent of  
20 prescriptions are written for patients under 65 who  
21 are usually medical beneficiaries due to emphysema  
22 disease or being disabled.

1           Seventy-two percent of prescriptions were  
2       for patients without cancer, and this was according  
3       to the cancer definition of having a cancer  
4       diagnosis in the same year as the prescription  
5       claim. If you use a broader definition of cancer,  
6       then it comes out to about 60 percent of  
7       prescriptions being for patients without cancer.

8           For context, you can see that TIRF, dozens  
9       have pointed out, is a tiny, tiny drop in the  
10      bucket of the larger opioid prescription picture.  
11      There are 372 million prescription claims  
12      [indiscernible] opioids, and that's written by  
13      2 million clinicians for 25 million patients.

14           On slide 6, you can see the overall  
15      prescribing rate, and you can see a very clear job.  
16      I'm just showing you this. This is broken down by  
17      brand as well as total prescribing as well. And  
18      you can see very obviously that right around TIRF  
19      implementation, there's a significant drop in  
20      prescribing. And after about a year, it starts  
21      rising and goes back close to the level where it  
22      was before. And you can see the breakdown, and

1 I'll let you pause [indiscernible] at that for a  
2 second.

3 Moving on to the next slide, here this is  
4 the time series results. Before REMS is  
5 implemented for March 2012, TIRF prescribing on the  
6 left side of the screen decreased by 1 percent per  
7 month. Right after REMS implementation, there's a  
8 27 percent decrease. I should say it's a level  
9 decrease, which means the way the time series  
10 analysis calculates it is the effects of REMS  
11 implementation resulted in a 27 percent decrease of  
12 the level of prescribing. But because of what  
13 happened a year later, it then results in a  
14 2 percent monthly increase in prescribing after  
15 about a year.

16 When you compare to all opioid prescribing,  
17 there is no significant trend pre-REMS  
18 implementation, and there is no change as a result  
19 of REMS implementation. But there is a decrease in  
20 all opioid prescribing following the REMS  
21 implementation, which you have to interpret this.  
22 And the interpretation I would have is that this is

1 not a result of REMS but simply the result of  
2 decreasing opioid prescribing overall, for the  
3 [indiscernible] population but overall in the  
4 country as well.

5 Next slide, please. These are additional  
6 descriptives for the secondary outcomes that I  
7 mentioned. There were no significant differences  
8 between over and under age 65 as a result of  
9 intervention [indiscernible]. The brand does not  
10 differ significantly either, and there are no  
11 significant differences when you exclude  
12 buprenorphine or the cold prep meds.

13 Next slide, please. You can see here that  
14 if you simply follow both lines, the top line is  
15 for patients without cancer. The bottom line is  
16 for patients with cancer, and this is a log  
17 prescription rate. All these analyses are adjusted  
18 for the increasing population. All these are late.  
19 And there is low difference between the two  
20 populations, so patients with cancer were affected  
21 similarly to patients without cancer, which is a  
22 possible adverse consequence of the REMS program.

1 That should be considered.

2 One other interesting finding for the  
3 overall prescribing rate is the decrease in  
4 prescription claims was associated with a very  
5 steep drop, as you can see for the bottom line.  
6 The top line is prescription claims, the bottom  
7 line is prescribers. The prescribers dropped  
8 pretty significantly. After about a year,  
9 prescription claims increased across the baseline,  
10 but the prescribers remained suppressed. It's  
11 something to consider.

12 Next slide, please. For outcome number 2,  
13 which was prescription cancer, here you can see  
14 that on the left side of the screen, it depends on  
15 how you define cancer. If you define cancer as  
16 having a diagnosis of cancer in the same year,  
17 there's a trend decrease for intervention. There  
18 is no change with intervention, and there's no  
19 significant change following the REMS  
20 implementation.

21 If you define cancer more broadly, that a  
22 patient has a cancer diagnosis at any point during



1       this study period, then the REMS implementation was  
2       associated with a 7 percent decrease in prescribing  
3       without cancer, but that also attenuated after  
4       about a year.

5               Next slide, please. Finally, the third  
6       outcome, we were measuring prescriptions to  
7       patients who are not opioid tolerant. So similar  
8       to -- the baseline is slightly lower than the  
9       previous data that was discussed, and I think it's  
10      because we use a much broader definition of opioid  
11      tolerance. It ranges, as you can see, at about the  
12      30 percent range. As a result of REMS  
13      implementation, I now could show that there's a  
14      23 percent decrease in prescribing to patients who  
15      are not tolerant and continued to decrease  
16      following REMS implementation.

17             Next slide, please. Limitations are that  
18      this obviously include Medicare Part D  
19      beneficiaries. We don't have data for  
20      out-of-pocket prescriptions. It's possible that  
21      some of those changes may have affected some of  
22      this, but some of those changes are [indiscernible]

1 mid-year.

2 We were lucky in this case that the  
3 implementation happened in March. By that point,  
4 all the [indiscernible] are usually frozen for the  
5 year, so this should not have affected this.  
6 People have mentioned [indiscernible] tolerance,  
7 and there again, I would say because of the time  
8 series analysis, the pre-intervention basically  
9 controls for that limitation.

10 In conclusion, our analysis shows for  
11 Medicare Part D beneficiary, REMS implementation  
12 resulted in a temporary decline in overall  
13 prescription claims. Most TIRF prescription claims  
14 were for patients without cancer. REMS  
15 implementation may have resulted, depending on how  
16 you define cancer -- [indiscernible] we've been  
17 prescribing patients without cancer. Finally, REMS  
18 implementation resulted in a lasting decrease in  
19 TIRF prescribing for patients who are not yet  
20 tolerant to opioids.

21 Next slide. Thanks to FDA CDER team who  
22 worked with me, as well as my co-authors Joseph

1 Ross and Nilay Shah. And I'll be happy to answer  
2 any questions in the question session. Thank you.

3 **Clarifying Questions**

4 DR. BATEMAN: Thank you.

5 We have 15 minutes for clarifying questions  
6 for the guest speakers. Please remember to state  
7 your name for the record before you speak, and if  
8 you can please direct your questions to a specific  
9 presenter. Dr. Brown?

10 DR. BROWN: Thank you. Dr. Fleischman, I'm  
11 interested in the data that you presented on slide  
12 7 regarding the TIRF prescription claims in 2010  
13 through '14 by brand. It appears that Subsys has  
14 become the market leader in the last several years,  
15 and I wondered if you have any comments about why  
16 that might be.

17 DR. FLEISCHMAN: I can't comment on why one  
18 brand took over another brand. I think  
19 that's -- the answer to that, I think, is something  
20 one can find. But I will just [indiscernible] that  
21 until around 2013, for the top-dashed line,  
22 [indiscernible] total prescription. The next line,

1 the black line, is the [indiscernible]. So for  
2 2014, the total line is essentially determined by  
3 the generic brand, generic fentanyl.

4 DR. BATEMAN: Dr. Meisel?

5 DR. MEISEL: Thank you. Steve Meisel with  
6 Fairview. A follow-up to the previous question.  
7 Knowing that Subsys, there's an anomaly here in  
8 terms of the data compared to everybody else, and  
9 we could speculate as to what's going on with the  
10 marketing of that product, if you were to pull  
11 Subsys from the other analyses with the  
12 prescriptions to patients without cancer and the  
13 percent of patients who are not opioid tolerant,  
14 and you pull stuff out of there and look at all the  
15 other TIRF, would there be a difference?

16 DR. FLEISCHMAN: You mean with prescribing  
17 the [indiscernible]?

18 DR. MEISEL: I'm looking at your  
19 slide -- it's hard to read the numbers here -- 13  
20 and slide 12, probably the two big ones here that  
21 apply, perhaps slide number 10, if you were to pull  
22 Subsys out of that and just look at the other

1 TIRFs, would those lines, the graphs look  
2 different? Is Subsys driving something here that  
3 is not apparent with the other TIRFs?

4 DR. FLEISCHMAN: Right. I've got your  
5 question. Those two outcomes actually cannot be  
6 measured or you can't really isolate -- Subsys is  
7 not [indiscernible] because Subsys -- well, I  
8 shouldn't say that. Subsys was out on the market  
9 when REMS was implemented. And I'm talking  
10 specifically about -- sorry. There are no claims  
11 for Subsys prior to TIRF implementation, which  
12 means that our question is essentially a  
13 before/after question, what effect does TIRF REMS  
14 have? And to answer that question, a brand  
15 that -- I cannot isolate and say Subsys did this or  
16 that because, obviously, there were no Subsys  
17 before that implementation.

18 We did not do a subanalysis where Subsys was  
19 taken out to see how the numbers changed. But I  
20 can tell you that -- we can't do [indiscernible]  
21 analysis for the most part because there's so few  
22 data points for each of the sub-brands. But that

1 is an interesting thing that we might consider  
2 doing in terms of isolating the data and running it  
3 again without certain brands in it.

4 DR. BATEMAN: I have a question for  
5 Dr. Jeffery, and it pertains to slide 17 from her  
6 presentation. So I'm wondering if you can help me  
7 understand this a little bit better. You were able  
8 to link 20,000 episodes where you had information  
9 on claims as well as the HR records. And of the  
10 9,245 patients with evidence of tolerance and  
11 claims, only 520 of those patients, when you  
12 reviewed the EHR, were you able to validate the  
13 presence of tolerance.

14 DR. JEFFERY: Yes, that's correct.

15 DR. BATEMAN: These data to me would  
16 suggests that the EHR are not particularly useful  
17 in establishing whether tolerance is present or not  
18 one way or the other. It's not just that you're  
19 not able to identify additional information  
20 supporting tolerance in those without evidence  
21 claims, but just that the EHR are not particularly  
22 informative.

1           Is that a fair conclusion?

2           DR. JEFFERY: Yes. This is one of the  
3           limitations of EHR data in general. We have this  
4           problem of leakage. And if we had a single EHR for  
5           the entire country, you wouldn't have this problem.  
6           So anytime you're going to do a study like this,  
7           you're going to be limited by the EHR information  
8           that you have available to you.

9           There was a small proportion where we were  
10          able to find evidence of tolerance. We have a  
11          slide -- if you go -- I don't know if you can pull  
12          it up, but it's like 26 -- sorry, 25. What this is  
13          showing you is the one that you just saw is in the  
14          top left. And then in the bottom right, what we've  
15          required is that we also saw a prescription for  
16          TIRF at the same time in the structured EHR. So  
17          that reduces our sample sizes even further, but we  
18          see about the same rate having additional  
19          information, and it is still small. It's smaller  
20          than the proportion of people who are non-tolerant  
21          for sure. I hope that helps.

22          DR. BATEMAN: Yes. Thank you.

1 DR. JEFFERY: Thanks.

2 DR. BATEMAN: Dr. Kulldorff?

3 DR. KULLDORFF: Thank you. I have a  
4 question about the last presentation. The key  
5 issue is how many of the people who get the drugs  
6 are actually getting it because they indicated  
7 versus contraindicated. There are two important  
8 factors. One is whether they have cancer or not,  
9 and the other one if they are opioid tolerant or  
10 not.

11 This presentation includes very important  
12 information on both those questions, but then the  
13 question is do you also have information on what is  
14 the proportion and percentage who both have cancer  
15 and are opioid tolerant, because there were other  
16 ones for which these drugs are indicated, while the  
17 others were 3 boxes or where they are  
18 contraindicated.

19 If we think that it is independent of each  
20 other, we can calculate that it will be about 22  
21 percent of the TIRF people who get it, who has it  
22 as an indication, but that independence might not



1       be true. So is it possible to use this data to get  
2       all these 4 boxes: cancer, tolerant cancer, not  
3       tolerant -- not cancer tolerant, and not cancer,  
4       not tolerant?

5               DR. FLEISCHMAN: That's a fair point. We  
6       may include that in our study that hopefully will  
7       be published. I will say that the numbers get  
8       relatively small, especially in the cancer  
9       population because most of the beneficiaries did  
10      not have cancer but who received the TIRF  
11      prescription. So the numbers may not -- we may not  
12      have statistically significant results on that, but  
13      I will consider including that in the descriptive  
14      results.

15             DR. KULLDORFF: And the numbers might not be  
16      sufficient to do the trend analysis and the  
17      comparison between pre- and post-REMS. But even  
18      the raw numbers over the last few years, over the  
19      time period, I think is interesting because that  
20      tells us whether these drugs are used for which  
21      this is indicated or not, in general, irrespective  
22      of REMS.

1 DR. FLEISCHMAN: Agreed, and we'll take a  
2 look at that.

3 DR. KULLDORFF: Thank you.

4 DR. BATEMAN: Dr. Habel?

5 DR. HABEL: Laurel Habel. I have a question  
6 for Dr. Fleischman, your patterns -- I realized  
7 that you looked at a different population than the  
8 FDA's utilization data. Your data's only on people  
9 over 65, but the patterns look different for both  
10 prescriptions and patients in that the FDA data  
11 looks like there's a downward trend that doesn't go  
12 back up.

13 I was just wondering if you thought about  
14 reconciling those two or if the FDA looked at that  
15 same age distribution, if they would see a similar  
16 pattern to the Medicare data or -- I was just kind  
17 of -- the patterns look different to me, and I  
18 don't know if you guys have thought about that.

19 DR. FLEISCHMAN: I didn't see the  
20 monthly -- I think I have some yearly data. I  
21 don't know if I remember the monthly data and how  
22 they differ. I agree that, certainly, the

1       age -- [indiscernible]. The FDA data looks at a  
2       much wider, a global prescription claims data.  
3       There definitely is a different population that  
4       probably explains in whatever way they differ.

5               DR. STAFFA: This is Judy Staffa. I would  
6       echo that. I think to remember that the Medicare  
7       data that Dr. Fleischman was looking at is not just  
8       those over 65 but also those covered by Medicare  
9       because of disability or end-stage renal disease.  
10      So it's a very different population than the global  
11      national estimates we're looking at.

12             DR. HABEL: But it does indicate that we may  
13      be seeing different patterns in different  
14      populations with respect to the declining  
15      prescriptions for these TIRFs.

16             DR. STAFFA: I think that's a fair point.

17             DR. HABEL: And I also had a question for  
18      Dr. Jeffery, and in a way, it's a little bit of a  
19      follow-up to the previous question. And that has  
20      to do with the very small percentage of individuals  
21      that were in that A box. And I thought you had  
22      said that your NLP was able to look at things like

1       prescriptions and doctor notes.

2               How did you actually validate that NLP  
3       algorithm? Because it would seem to me that if you  
4       got a prescription for one of those drugs, there  
5       would be something in the notes, and it wouldn't  
6       be -- it looks like it's only about 5 percent or  
7       something of the patients that have a claim also  
8       had some evidence when using NLP that they've been  
9       prescribed one of these drugs.

10              Anyways, I was just kind of wondering how  
11       you did that.

12              DR. JEFFERY: Thanks. This is Molly  
13       Jeffery. It's a complexity of the data that we  
14       have, and I wasn't able to present in enough detail  
15       maybe to make this completely clear. We have some  
16       people for whom we have both structured EHR data  
17       and notes and some people for whom we do not. We  
18       only have structured data. The notes population is  
19       considerably smaller than the proportion of people  
20       who have structured data.

21              When we're looking in the structured data  
22       for evidence of tolerance, the reason that it will

1 look so small there compared to what we can see in  
2 claims is that the only thing we can see in EHR  
3 data is what happens within that system. And we  
4 know that people receive their healthcare from many  
5 different systems. So in cases where there are  
6 notes, you would think that you would be able to go  
7 in there and find great information where the  
8 physician says we did this because such and such.  
9 But to protect patient privacy in research, we are  
10 not able to actually go in and read the notes. We  
11 can only use the NLP summary for the most part. So  
12 it's not like doing a chart review, unfortunately.

13 DR. HABEL: So in a closed system, an NLP  
14 algorithm might work better. In this data that you  
15 had, it maybe doesn't work very well. I'm just  
16 trying to figure out if there are other data  
17 sources for which the yield might be better with  
18 the EHR. Okay. Thank you.

19 DR. JEFFERY: If I can answer that, I think  
20 within a closed system, you would be quite a bit  
21 better often, especially if you could do a chart  
22 review. I would say, though, that the structured

1 data is going to be your best source of it because  
2 if you're looking for opioid tolerance, what you  
3 want to know is was the person taking prescription  
4 opioids.

5 We exclude people who were in the hospital,  
6 so it's not like we're going to get information  
7 from the hospital record. What we're really  
8 looking for the most part are prescriptions because  
9 it's very difficult to think of any other ways  
10 somebody could be opioid tolerant other than  
11 receiving opioids in the hospital or receiving  
12 prescription opioids.

13 So we can considered the idea that somebody  
14 could have opioid-use disorder and could be using  
15 illicit opioids, but then are they really a great  
16 candidate for receiving one of the REMS drugs?  
17 It's probably going to be difficult for a physician  
18 to believe that. So yes. I think that within a  
19 closed system, it would be great. The problem with  
20 a closed system is that now you've seen one system.  
21 When you've seen one healthcare system, you've seen  
22 one healthcare system.

1           So it's a limitation of the types of data  
2       that we have available to us in the United States,  
3       unfortunately. We just have to take the best that  
4       we can from every different kind of data that's  
5       available to us and try to make the full picture by  
6       bringing all those things together.

7           DR. HABEL: Thank you.

8           DR. BATEMAN: Dr. Katzman?

9           DR. KATZMAN: Thank you. I have just two  
10       very quick questions for Dr. Fleischman. On slide  
11       6 on the results descriptive, I was just impressed  
12       by the 72 percent of the prescriptions were for  
13       patients without cancer. And I was just wondering  
14       if you perhaps had -- if you were able to do a  
15       deeper dive to what other diagnoses these patients  
16       had besides a cancer diagnosis.

17          DR. FLEISCHMAN: We did not. We did not do  
18       an in-depth analysis. I think in reviewing those,  
19       79 percent of the prescriptions are for patients  
20       who likely have -- who have Medicare coverage or  
21       Part D coverage from being disabled or  
22       [indiscernible]. And I think that gives you a clue

1       for what the likely diagnoses are.

2               DR. KATZMAN: Thank you. My second and last  
3       question pertains to slide 11. I was impressed by  
4       the slide that is entitled, Prescriptions and  
5       Prescribers, showing the drastic reduction in  
6       number of prescribers of these TIRF medications  
7       beginning in the year 2012. And yet, the number of  
8       prescriptions falls off in 2012 for a year, but  
9       then it goes back up. And yet, the number of  
10      prescribers stays significantly low.

11             I just wanted to know if you had any  
12      thoughts about that.

13             DR. FLEISCHMAN: I think it's an incredibly  
14      important point, especially as we look to intervene  
15      directly with certain prescribers who may have  
16      dangerous prescribing practices. And one thing  
17      that's very notable with TIRF prescriptions is that  
18      there were some prescribers who dominated the  
19      prescribing of certain TIRF drugs. And it is -- if  
20      you look at the data in a whole, and you look at  
21      that slide and you look at the slide of the  
22      increasing -- if you combine that with the slide



1       that shows the breakdown and how it increases, the  
2       breakdown by brand and how it increases power and  
3       [indiscernible], I think it is worrisome and  
4       something to follow up on. I think [indiscernible]  
5       followed up on is all I'll say.

6               DR. KATZMAN: Thank you. Thanks so much.

7                       **Open Public Hearing**

8               DR. BATEMAN: We now need to move to the  
9       open public hearing session, and we'll have time to  
10      return for clarifying questions once that's  
11      completed.

12              Both the Food and Drug Administration and  
13      the public believe in a transparent process for  
14      information-gathering and decision-making. To  
15      ensure such transparency at the open public hearing  
16      session of the advisory committee meeting, FDA  
17      believes it's important to understand the context  
18      of an individual's presentation.

19              For this reason, FDA encourages you, the  
20      open public hearing speaker, at the beginning of  
21      your written or oral statement to advise the  
22      committee of any financial relationship that you

1       may have with the sponsor, its product, and if  
2       known, its direct competitors. For example, this  
3       financial information may include the sponsor's  
4       payment for your travel, lodging, or other  
5       expenses in connection with your attendance at the  
6       meeting. Likewise, FDA encourages you at the  
7       beginning of your statement to advise the committee  
8       if you do not have such financial relationships.  
9       If you choose not to address this issue of  
10      financial relationships at the beginning of your  
11      statement, it does not preclude you from speaking.

12               The FDA and the committee places great  
13      importance in the open public hearing process. The  
14      insights and comments provided can help the agency  
15      and these committees in their consideration of the  
16      issues before them.

17               That said, in many instances and for many  
18      topics, there will be a variety of opinions. One  
19      of our goals today is for the open public hearing  
20      to be conducted in a fair and open way, where every  
21      participant is listened to carefully and treated  
22      with dignity, courtesy, and respect. Therefore,

1 please speak only when recognized by the  
2 chairperson. Thank you for your cooperation.

3 Will speaker number 1 step up to the podium  
4 and introduce yourself? Please state your name and  
5 any organization you're representing for the  
6 record.

7 DR. FOX-RAWLINGS: Thank you for the  
8 opportunity to speak today on behalf of the  
9 National Center for Health Research. I am  
10 Dr. Stephanie Fox-Rawlings. Our center analyzes  
11 scientific and medical data to provide objective  
12 health information to patients, health  
13 professionals, and policy makers. We do not accept  
14 funding from drug or medical device companies, so I  
15 have no conflicts of interest.

16 Our center worked with Congress to create  
17 the REMS program and legislation that became law  
18 quite a few years ago. The goal was always to  
19 enable FDA to approve effective drugs even when  
20 they had worrisome risks. The REMS were intended  
21 to lower those risks as much as possible so that  
22 patients taking the drugs were the most likely to

1 be helped and least likely to be harmed. A major  
2 shortcoming of these risk mitigation strategies has  
3 always been ensuring that they are effective in  
4 lowering risks. It is difficult to evaluate the  
5 effects of the REMS on prescribers, pharmacists,  
6 patients, and others who accidentally or  
7 intentionally misuse drugs.

8 The data before you today that evaluated  
9 these REMS is limited, however, we commend the  
10 efforts of TRIG and the FDA to assess these REMS  
11 and to improve the data as well as the  
12 effectiveness of the REMS. We strongly urge that  
13 TRIG implements the FDA's recommendations in a  
14 timely and complete manner to more fully understand  
15 to what extent the REMS are and are not working, so  
16 that they can increase the benefit-risk ratio of  
17 their products.

18 The data are especially limited regarding  
19 the proportion of prescriptions for cancer pain or  
20 other indication. So it's a big problem since this  
21 product is only approved for cancer pain. And like  
22 the FDA reviewers, we are very concerned about the

1 increased risk of adverse events after implementing  
2 REMS. Even though the reports are voluntary and  
3 therefore could be biased, the increase after REMS  
4 is very disturbing.

5 The quality of the REMS data is also low  
6 because only a subset of potential events are  
7 evaluated. This makes the data difficult to  
8 interpret. However, other sources of data also  
9 suggests there are concerning numbers of  
10 therapeutic errors, misuse, and exposures with  
11 serious consequences.

12 Congress supported REMS because they were  
13 intended to reduce the risk of serious harms while  
14 continuing to make the product available to those  
15 who need it. The data indicate these REMS need  
16 improvements. For example, 42 percent of users  
17 were not opioid tolerant. This increases the risk  
18 for central nervous system and breathing problems,  
19 and a relatively high proportion of survey  
20 respondents did not know the correct indication or  
21 that TIRFs needed to be stopped if around-the-clock  
22 opioid medication is stopped. They learned this in

1 the training but cannot remember it later on.

2 Changes to REMS should be designed to make  
3 them more effective at protecting patient. Changes  
4 in REMS should not be aimed primarily at increasing  
5 the number of prescriptions. An increase in  
6 prescriptions without ensuring appropriate  
7 prescribing, dispensing, use, and disposal  
8 increases the risk that more patients will be  
9 harmed and that the drugs will be used accidentally  
10 or misused by individuals who are not prescribed  
11 it.

12 The bottom line, TIRFs provide important  
13 options for cancer patients dealing with pain.  
14 However, we all know that they carry very serious  
15 risks, and that's why we need the REMS to protect  
16 patients from these. These REMS are not working as  
17 well as they could or should be to protect patients  
18 and can be improved. Thank you.

19 **Clarifying Questions (continued)**

20 DR. BATEMAN: The open public hearing  
21 portion of this meeting is now concluded, and we'll  
22 no longer take comments from the audience. The

1       committee will now turn its attention to address  
2       the task at hand, the careful consideration of the  
3       data before the committee as well as the public  
4       comments. Before we do that, I think we're going  
5       to return to clarifying questions, first for the  
6       guest speakers and then for the TRIG.

7               For the guest speakers, the next person to  
8       ask questions is Dr. Warner.

9               DR. WARNER: Thank you. Margaret Warner  
10       from the National Center for Health Statistics. I  
11       wanted to follow on, on the questions to  
12       Dr. Jeffery about the methodology with the natural  
13       language processing. I know you've tried to  
14       explain a little bit more about the method you  
15       used. I was surprised that you weren't able to  
16       look actually at the notes themselves because that  
17       makes natural language processing very difficult,  
18       but was wondering whether you were able to validate  
19       it in any other way, in other data sources to see  
20       if it was a good method to use in the future.

21               I was surprised, like I think the other  
22       panelists alluded to, that you had the low

1       agreement even in that A box. So I just wanted to  
2       give you a chance to explain a little bit more.

3               DR. JEFFERY: Sure. Thank you. The way  
4       that the natural language processing analysis works  
5       is it is a type of artificial intelligence, and it  
6       is the type that is unsupervised. What that means  
7       is that we are not interacting directly with the  
8       text. The algorithms are interacting with the  
9       text. And what we did specifically is we said, in  
10      the 30 days prior to your first fill of one of  
11      these drugs, the OTO drugs, we gathered all of your  
12      notes into one long document, and then we run the  
13      algorithm on it.

14             What it does is it sifts through and sort of  
15      summarizes a document by identifying important  
16      words and phrases that are called terms, so it  
17      could be several words together, that appear to be  
18      specific to that particular document. But they  
19      can't be unique to that document. So we're not  
20      interested in names or the name of a clinic and  
21      things like that. So we sift through that in  
22      advance, taking out things like names. We feed it



1       into the algorithm. The algorithm summarizes it  
2       and gives us back topics.

3               I do actually have a slide of this. It's  
4       like the last couple -- maybe the last two slides  
5       in my deck. I don't know if they can bring it up.  
6       But it gives you an example of how a particular  
7       episode was summarized into topics, and then what a  
8       sample of one of those topics looks like so you can  
9       kind of see what the output is.

10              This is an example of a note -- go back to  
11       the previous one that you were just on. This is an  
12       example of a particular note. It had topics that  
13       were assigned to it, and those are the columns  
14       going across in the bigger left-hand box. The  
15       tallest of those is the topic lab tests, which you  
16       see up in the top. When the analysis is actually  
17       done, it doesn't spit it out and say this is the  
18       lab tests topic. We actually did that as  
19       researchers and with our technical expert panel.

20              If you can go to the next, please. This is  
21       an example of what a topic looks like. The topics  
22       are made up of terms. The tallest term here was

1       pancreatic. And then you can see that there are  
2       lots of other words along there that sort of have  
3       things to do with pancreatic cancer, the types of  
4       treatments you would receive for that, et cetera.

5               So this particular document, this particular  
6       topic, means pancreatic cancer. That's the name we  
7       assigned to it. If you can go back to the previous  
8       one. So each of the notes has several of these  
9       topics that are assigned to it.

10              That's kind of what the NLP comes out with.  
11       We don't have access to the exact document,  
12       although there was one member of the team that  
13       could see the real stuff, but it was behind kind of  
14       a Chinese wall, so we could not see them as  
15       researchers to protect patient privacy.

16              Does that help at all?

17              DR. WARNER: Yes, quite a bit. I thought  
18       you started with asking the clinicians to come up  
19       with lists of words, and doing some kind of search.  
20       But this is --

21              DR. JEFFERY: That was part of it as well.  
22       One of the things that we had always planned to do

1       was this NLP, where we would summarize. And then  
2       for every episode, we would summarize this one got  
3       lab tests and pancreatic conditions, and then we  
4       would spit that back into the claims section and  
5       run it again.

6               As we were going through, we were finding  
7       these very high rates of non-tolerance, so we  
8       started asking our tech [ph] members why could this  
9       be happening, what should we be looking for in the  
10      notes that would tell us why somebody's getting a  
11      drug that they are not opioid tolerant and they  
12      should be. So at that point, we created this white  
13      list of words where we said, well, if you're going  
14      to get a fentanyl patch, maybe somebody is  
15      concerned that you have stomach issues and you  
16      can't absorb gastrointestinally. So maybe that's  
17      why they've given you the fentanyl patch.

18             So we in addition had that white list of  
19      words that was purely generated by human beings  
20      based on their knowledge. We checked both, the  
21      results of the NLP and the results of those  
22      white-listed terms, and neither of them showed any

1       associations with having or not having evidence of  
2       tolerance.

3               DR. WARNER:   Can I have one last question  
4       about this?   From your comments, several times  
5       you've mentioned that you -- I can't remember the  
6       words; leakage, that these people were going to  
7       other places.   And that seemed to be your  
8       explanation for the lack of agreement.   And I'm  
9       wondering -- I know that in some more recent EHRs,  
10      they have continuing care documents so that you  
11      would have information.   Even though the patient  
12      wasn't in that EHR, they actually have information  
13      from other vendors or during their other visits.

14             Did you have access to that information for  
15      this analysis?

16             DR. JEFFERY:   We did not, and we were using  
17      the previous 10 years, so 2007 to 2016.   I think it  
18      will be a feature of future research to try to  
19      gather information like that, and there are some  
20      platforms out there that do that.   But we did not  
21      have access to that here.

22             DR. BATEMAN:   Dr. Sandbrink.

1 DR. SANDBRINK: Friedhelm Sandbrink from the  
2 Department of Veterans Affairs. I have two  
3 questions, really. One is for Dr. Jeffery. It's  
4 really in follow-up to this. It's going to be a  
5 brief question.

6 I see that in our table when we look at  
7 that, you're looking for evidence for tolerance.  
8 And anybody where you can't find the evidence,  
9 you basically conclude that they're probably  
10 non-tolerant; I don't have evidence for what they  
11 truly are.

12 I'm wondering if you could basically  
13 rephrase your question to the EHR and ask do I have  
14 evidence that this patient truly is not tolerant?  
15 You see? It's a reverse question because we're  
16 going away from all these patients that we can't  
17 see tolerance and say we don't really know about  
18 them. But what fraction of those do we have clear  
19 evidence that they are not tolerant? And that  
20 could be documented in the chart at somebody's  
21 writing I'm starting this new medication in this  
22 patient who didn't have prior opioid therapy. So

1       that's one question.

2               DR. JEFFERY: It's a great approach. It  
3       would be wonderful to do. You would really need to  
4       have chart access, though. You would need to have  
5       complete access. And as we were talking to  
6       physicians about how they document, we did not hear  
7       from them that they would write something like  
8       that.

9               So maybe if there was some kind of pop-up,  
10       there was a CDS [ph] that said this person is not  
11       opioid tolerant, why are you giving them fentanyl,  
12       and you had to write in a reason, that would be  
13       specific to an individual system in EHR. But in  
14       general, we did not.

15              The other piece of it, though, is that if  
16       there were such a thing, if there were people  
17       saying this person is not opioid tolerant, but I'm  
18       doing this because, then we could have picked that  
19       up in the NLP, but we did not. So it's not  
20       proof -- absence of evidence is not evidence of  
21       absence, but to the extent that we can say that we  
22       did not see anything like that.

1 DR. SANDBRINK: Thank you. And my second  
2 question is both to you, Dr. Jeffery, and  
3 Dr. Fleischman. I'm intrigued by the data that  
4 show Optum and CMS data, 72 percent are non-cancer  
5 patients. And I'm wondering how much that is  
6 reflective of the prescribing as a whole, realizing  
7 the CMS specific data. And I feel that, obviously,  
8 your data set for Optum could give us an answer of  
9 whether in this very different population, again,  
10 the majority of prescribing is in non-cancer  
11 patients.

12 Related to that -- and that maybe goes to  
13 CMS, is the question, is there a difference in the  
14 prescribing pattern actually in regard to the  
15 dosages, in regard to the trajectory of increases  
16 over time, and maybe also the duration of  
17 prescribing? If you have a patient who is on  
18 medication over many, many, many years, it's  
19 probably not an rapidly advancing cancer.

20 So I'm wondering whether a lot of the  
21 changes that we see in the prescribing pattern is  
22 related to possibly the vast majority of the

1 patients who were on this medication in the past  
2 and who are not [indiscernible] non-cancer  
3 patients, where prescribers are just getting a  
4 whole lot more careful, realizing that these are  
5 not the patient that these medications are  
6 indicated for.

7           Maybe in this regard, I think there's a  
8 little bit of a clarification that maybe I need to  
9 have also. Again, the difference between what it's  
10 indicated for and what it's contraindicated for. I  
11 think we have these very hard requirements not to  
12 prescribe this in a patient who is a child, and we  
13 are not prescribing in a patient who is not  
14 tolerant. But in regard to the non-cancer  
15 patients, the language is much more weight. It  
16 talks about what is indicated for the cancer  
17 patient, but it doesn't say that you cannot  
18 prescribe it a non-cancer patient the same way as  
19 it's very clear that you can't do it in a child or  
20 in somebody who is not opioid tolerant.

21           So I feel that we need to separate those. A  
22 lot of the information that comes about what



1 providers know about it, providers who take this  
2 training, they presume that we all know that this  
3 is for cancer patients. But the reality is the  
4 majority don't seem to be cancer patients. Are  
5 these legacy patients? Are they patients that were  
6 started on many, many years ago? Is a trajectory  
7 of them gradually coming off?

8           Anyway, that's why I'm wondering if a larger  
9 data set such as Optum [indiscernible] could help  
10 us in that regard.

11           DR. JEFFERY: Shall I take that? Okay.

12           This would be a perfect question that we  
13 could look into in our data set. So in addition to  
14 the Medicare fee for service that you've already  
15 seen from Dr. Fleischman, it would be very possible  
16 to look at the commercially insured and the  
17 Medicare Advantage populations. And then that  
18 covers a large proportion of the United States. So  
19 that would certainly be something that we can do.

20           One thing that I would say is that the  
21 information that we had the best -- the thing that  
22 we could look into the best was fentanyl patches

1       because there were the most of them in our sample.  
2       And we did not specifically look for cancer because  
3       the TIRFs were only a small part of our overall  
4       study. But we did look at something else, which  
5       was to what extent does this appear to be like a  
6       calculated risk sort of.

7               So we provided information by dose for you  
8       for TIRFs. And if you remember, it was relatively  
9       the same, except for the very highest dose. That  
10      looks different in fentanyl patches. In fentanyl  
11      patches, the evidence of tolerance is much lower at  
12      12 and a half micrograms, and it goes up as the  
13      dose gets higher. So in that way, these two types  
14      of products are not being prescribed in the same  
15      way.

16             DR. BATEMAN: Dr. Fry?

17             DR. FRY: Michael Fry, Providence Health and  
18      Services Oregon. This question goes this morning  
19      for TRIG, specifically I guess maybe Mr. Sherman.

20             You're looking at things --

21             DR. BATEMAN: Dr. Fry, I think we want to  
22      finish up with the questions for the guests

1 speakers --

2 DR. FRY: Okay. Sorry.

3 DR. BATEMAN: -- and then we'll return to  
4 the TRIG questions.

5 Dr. Brand, did you have a question for the  
6 guests?

7 DR. BRAND: Thank you. This question is  
8 actually for both Dr. Jeffery and Dr. Fleischman  
9 just because you're presenting claims data. As a  
10 pharmacist in the trenches, I'm wondering how many  
11 of those claims were rejected because they didn't  
12 have the right diagnoses. I know these medicines  
13 are not inexpensive, so they probably required a  
14 prior authorization.

15 So I guess I'm wondering with such a high  
16 rate of non-cancer diagnoses, how did they get  
17 through the claims in the first place?

18 DR. JEFFERY: That's question for me?

19 DR. BRAND: Certainly.

20 DR. JEFFERY: I don't know the details of  
21 what kind of prior auth programs were in place for  
22 the claims that we looked at. I do know that it

1       would be different. So like the Medicare Advantage  
2       might all look relatively similar to each other,  
3       but there are also groups where the company behind  
4       this is providing administrative services only.  
5       And in that case, it would be like an employer  
6       hires them just to administer it. And in that  
7       case, they get to set their own prior auth  
8       requirements and all of that.

9               So it varies within our data set. We only  
10       included claims that were paid, and we do not,  
11       unfortunately, see any evidence that somebody tried  
12       to have it paid for, but due to a prior auth  
13       restriction was turned down.

14              DR. FLEISCHMAN: I'll echo the same thing  
15       with Part D data. This is only claims that were  
16       paid. A claim that was not paid, like a tree  
17       falling in a car, it does not show up in any data;  
18       well, in this data anyway. And CMS does not  
19       even -- well, CMS itself does not have this data,  
20       but the other drug plans do. The drug plans  
21       probably do have the data, but CMS does not have  
22       it.

1           You had a -- just a comment, a question  
2       there. This data does not judge the other  
3       physicians -- what the clinicians prescribe  
4       fentanyl for patients who have cancer. Our study  
5       was simply looking at what the effect of  
6       [indiscernible] patient was. We just simply took  
7       the two main points of the educational materials  
8       that prescribers take, hopefully they go through,  
9       and tested them.

10           So I am not making a judgment, and we are  
11       not making a judgment about whether it should be  
12       prescribed off label or not. That's a whole  
13       separate discussion.

14           DR. BATEMAN: I have question for  
15       Dr. Jeffery regarding your claims-based analysis.  
16       Did you look at the patterns of opioid filling in  
17       the 39 percent that were deemed not tolerant? I'm  
18       wondering what percentage of those patients are  
19       regularly taking opioids but perhaps not as the  
20       dose threshold that would qualify them as being  
21       tolerant.

22           DR. JEFFERY: We did not. We did only to

1 the extent that we had the four different  
2 definitions of tolerance. And the least stringent  
3 of them looked for any 7 days in the prior 30. But  
4 I will say that the patterns of -- you were more  
5 likely to be tolerant with those different  
6 descriptions, but everything was similar otherwise.  
7 It just raised the level. But we did not do any  
8 subset analysis of different patients other than to  
9 look at commercial versus Medicare Advantage.

10 DR. BATEMAN: What percentage were deemed  
11 not tolerant when you used the loosest definition  
12 of tolerance?

13 DR. JEFFERY: Unfortunately I don't know if  
14 I have that in a separate slide. Oh, I do actually  
15 for TIRFs. I do have it for TIRFs. It's slide 23.  
16 This is what it looks like.

17 Primary tolerance is the one we discussed.  
18 It is at least 30 milligrams of oxycodone  
19 equivalent in 7 consecutive days just leading up to  
20 the secondary; again, required the 30 milligrams.  
21 But it had just any 7 days out of 30; tertiary, no  
22 dose requirement but had to be taking opioids in

1 the prior 7 days. And then the quaternary was any  
2 milligrams of opioids in 7 out of the prior 30. So  
3 you can see, they're fairly similar results.

4 DR. BATEMAN: Thank you.

5 Are there any additional questions for the  
6 guest speakers? Dr. Arfken?

7 DR. ARFKEN: I'm not sure either of the  
8 speakers could address this, but I was wondering if  
9 it was possible to determine, for example, that the  
10 people without cancer had a life expectancy of less  
11 than 6 months.

12 DR. JEFFERY: For us, we did not look at  
13 cancer because we had the four products.

14 DR. ARFKEN: No, but in non-cancer patients,  
15 that they were in palliative care.

16 DR. JEFFERY: Right. We didn't exclude  
17 people based on that. We were looking for  
18 hospitalizations in the prior 30 days, though, and  
19 that dropped about 20 percent of our total claims  
20 samples. So many of them could have been in that  
21 group.

22 DR. FLEISCHMAN: We had no persons for

1 palliative care and hospice in this study. We  
2 could -- the data that we have now would not have  
3 it, but we could certainly dive in to  
4 [indiscernible] data, but this is beyond the scope  
5 of this study.

6 DR. BATEMAN: Okay. We're now going to move  
7 back to clarifying questions for the TRIG. Dr.  
8 Nelson? No? Okay.

9 Dr. Joniak-Grant?

10 DR. JONIAK-GRANT: Elizabeth Joniak-Grant.  
11 I have a couple of questions. My first question  
12 is -- and Dr. Mariano's presentation on his slide  
13 27, it talks about mandatory patient education, and  
14 I was wondering how mandatory patient education is  
15 carried out.

16 Then my second question will be about -- I  
17 want to know what these knowledge assessments that  
18 the prescribers and pharmacists have to score 100  
19 percent on, what those look like.

20 MR. SHERMAN: Dr. Mariano?

21 DR. MARIANO: From the standpoints of the  
22 education that the patients actually undergo, it's



1 the PPAF form, the physician-patient  
2 acknowledgement form. It basically has all the  
3 information and the do's and don'ts of using the  
4 TIRF products and what they need to do from a  
5 safety standpoint, how they need to secure the  
6 medications, and all that information that the  
7 physician goes over. And then the patient signs  
8 and acknowledges that that information has been  
9 given to them, and they get to take that home with  
10 them as well, a copy of that.

11 DR. JONIAK-GRANT: So is it mandatory for  
12 the prescriber to read it to the patient?

13 DR. MARIANO: That would be -- when I did  
14 it, the answer was yes. Now, is it the physician?  
15 Is it the nurse practitioner in the practice? Is  
16 it the medical assistant? I can't answer that. It  
17 has to be done with the patient, and then the  
18 physician or the person who's prescribing should  
19 answer and clarify any risk-benefit questions with  
20 the patient.

21 DR. JONIAK-GRANT: Okay. And then for the  
22 knowledge assessments?

1 DR. MARIANO: And there's also the  
2 medication guide. I do apologize, as well, that  
3 they do receive --

4 DR. JONIAK-GRANT: But basically, it's  
5 pieces of paper that they may just get handed --

6 DR. MARIANO: No. Actually, the  
7 physician --

8 DR. JONIAK-GRANT: -- and they hope that you  
9 read them.

10 DR. MARIANO: No. The physician does go  
11 over the information with the patient, and they may  
12 actually read the form with them, and then the  
13 physician comes in after the fact and goes through  
14 the questions again and explains any information  
15 they do not understand because they do have to sign  
16 it along with the physician at the practice. And  
17 when I did mine, it was literally I went over the  
18 information with the practice. I just can't tell  
19 you for every single prescriber out there.

20 DR. JONIAK-GRANT: Right. I was just  
21 wondering, because I know whenever I read forms  
22 that I have to sign at doctors' offices, they kind

1 of laugh and say people don't do that very often.

2 DR. MARIANO: But to go home with your  
3 prescription, that's part of the whole process of  
4 getting your prescription for your TIRF project.

5 DR. JONIAK-GRANT: But you just said you  
6 weren't sure if they went over it with them, and  
7 now I feel like you're saying they definitely go  
8 over it with them.

9 DR. MARIANO: I didn't say that. I said I  
10 don't know if they actually are the ones who were  
11 specifically reading the entire form to them, and  
12 then come in for clarifying afterwards, or they do  
13 the entire form with them in the beginning. I  
14 can't answer for every specific physician.

15 DR. JONIAK-GRANT: Okay.

16 DR. MARIANO: But the rule of thumb is that  
17 the patient-provider who's prescribing the TIRF  
18 product goes over the form with the patient.

19 DR. JONIAK-GRANT: They do?

20 DR. MARIANO: Dr. Pergolizzi, do you have  
21 anything else to add with this?

22 MR. IRWIN: This is Kyle Irwin. The patient

1       prescriber form is also available on the website  
2       where the prescriber and patient can go through and  
3       do it electronically to expedite the process, in  
4       addition, as another option alternative to the  
5       paper form.

6               DR. BATEMAN:   Dr. Meisel?

7               DR. JONIAK-GRANT:  I'm sorry.  I had one  
8       more question, the one I asked before about the  
9       knowledge assessments that they have to score 100  
10      percent, what exactly are those and what do they  
11      look like.  Because they're scoring 100 percent,  
12      and then it seems to fall off quite a bit.  I'm  
13      curious as to how the assessments --

14              MR. SHERMAN:  The questions are right here.  
15      We'll go through them.

16              DR. MARIANO:  I can show you all 11  
17      questions if that's what you prefer.

18              DR. JONIAK-GRANT:  I'm just trying to figure  
19      out the format.  Is it something you read a  
20      paragraph, and then you go to the next slide, and  
21      then you answer a question, for example.  Sometimes  
22      they're done that way.  How are they carried out

1 and scored?

2 MR. SHERMAN: I'm going to let Amanda from  
3 McKesson address your question.

4 MS. BULKLEY: So they do have to complete an  
5 education packet first. and on the website, the  
6 way that looks is they go through the entire  
7 education before they propose the questions and  
8 answers. The questions are multiple choice. There  
9 are 11 questions. They are statements with, I  
10 believe, 4 to 5 answers in the multiple choice  
11 selection.

12 DR. JONIAK-GRANT: Sorry, just to follow up.  
13 And overall, how long would you say it takes for  
14 someone to complete one of these?

15 MS. BULKLEY: Estimation is about 30 minutes  
16 through the education and the knowledge assessment  
17 itself. And I do want to point out that you cannot  
18 go back on the website when you're performing the  
19 knowledge assessment for the website itself.

20 DR. JONIAK-GRANT: Thank you.

21 DR. BATEMAN: Dr. Meisel?

22 DR. MEISEL: Question, and this will be

1       quick for Dr. Stemhagen on some of the outcomes. I  
2       think I know the answer.

3               In the deaths that were reported, do you  
4       have any knowledge as to how many were suicide  
5       versus accidental versus underlying disease versus  
6       side effect? And how many may have been in  
7       patients without cancer versus those who were with  
8       cancer?

9               MR. SHERMAN: Dr. Stemhagen?

10              DR. STEMHAGEN: We don't have all of that  
11       information. We can get the suicide information,  
12       but a lot of the others, it's just not provided in  
13       a lot of the reports. That's the very difficult,  
14       frustrating limitation of these reports.

15              DR. MEISEL: Then the other question, is  
16       there any way to divvy out Subsys versus the other  
17       TIRF products within this in terms of number of  
18       deaths related to Subsys versus the others?

19              DR. STEMHAGEN: In the whole analysis, we  
20       don't separate it out by product, but certainly the  
21       sponsor would get the reports. The other  
22       difficulty that we find is many sponsors have a

1 procedure in place. So if a report comes to them  
2 and it says fentanyl, even if they don't know it's  
3 their product, they feel obligated to report it to  
4 FDA to make sure that it gets reported. So we  
5 can't always distinguish illicitly manufactured  
6 fentanyl from the actual products.

7 DR. BATEMAN: Dr. Goudra?

8 DR. GOUDRA: Basavana Goudra from pain  
9 medicine. If I refer back to this morning's  
10 presentation, CC-26, Dr. Pergolizzi. Can you  
11 please explain what really -- now, this is quite a  
12 contrast between the U.S. and Western Europe. Is  
13 there a difference in indications for the use of  
14 TIRFs? Are there any differences in the regulatory  
15 hurdles or is there any cost difference? What  
16 explains this? I guess the patient population is  
17 very similar.

18 MR. SHERMAN: The indications are the same.

19 DR. GOUDRA: Are you saying it's still only  
20 cancer patients who are tolerant opioids?

21 MR. SHERMAN: Correct. Actually, the  
22 biggest difference there is 6 branded products and

1       4 generics in the U.s.   There's 3 TIRF products in  
2       the EU.

3               DR. GOUDRA:   The cost is much different.

4               MR. SHERMAN:   Pardon?

5               DR. GOUDRA:   The cost is much different.

6               MR. SHERMAN:   That's one piece of  
7       information I don't have, but I'll let Dr. --

8               DR. GOUDRA:   What other regulatory hurdles?  
9       Are there same problems like here?   What are the  
10       regulations to use this?

11               MR. SHERMAN:   There's not a TIRF REMS, but  
12       they're restricted.   So there's a little difference  
13       there.

14               DR. GOUDRA:   So what do you think explains  
15       the big difference?

16               MR. SHERMAN:   I'll let Dr. Pergolizzi answer  
17       that part.

18               DR. PERGOLIZZI:  If you look at some of the  
19       European cancer guidelines and palliative cancer  
20       guidelines, you'll see that they're moving away  
21       from the standard WHO step ladder.   And actually,  
22       even when it comes to managing chronic, persistent



1 cancer pain, they're using the more potent agents,  
2 which would normally be step 3's at lower doses and  
3 titrating up.

4 At the same time, I think they become more  
5 aware of the three primary classifications of  
6 cancer pain, which are the chronic, persistent  
7 cancer pain; intermittent pain; and then  
8 breakthrough cancer pain. I think they're trying  
9 to do a much better job at addressing the  
10 breakthrough cancer pain, and that's why you see  
11 the differences between here and Europe from the  
12 prescribing, overall number of units prescribed.

13 As far as payment goes, again, this is  
14 western EU. Each country's going to have its own  
15 type of reimbursement system, so it's hard for me  
16 to speculate on what's happening in each country.  
17 But a lot of them do have universal health care as  
18 well. Some like in Germany will have a rider  
19 policy of private healthcare to supplement that as  
20 well.

21 DR. GOUDRA: Just one more question. As you  
22 already presented, the top medications used,

1 [indiscernible] has come down drastically here. Is  
2 it likely that clinicians have found other ways of  
3 addressing the pain, like non-opioids or gabapentin  
4 or pregabalin, ketamine or anything like that?

5 DR. PERGOLIZZI: When we look at the  
6 anti-hyperalgesics, gabapentin, duloxetine, these  
7 agents usually require some time to titrate up to  
8 an effect. So with breakthrough cancer pain, it's  
9 a spontaneous unevoked or evoked pain that happens,  
10 a very rapid onset, very peak. So administering a  
11 gabapentin or a pregabalin or duloxetine would not  
12 be able to handle that.

13 Other anti-hyperalgesics, if you have a  
14 broader class, might be using a ketamine type  
15 product or using a local anesthetic. But again,  
16 that could be very impractical, and normally it  
17 won't happen with self-administration at home,  
18 et cetera.

19 Again, there are some differences in  
20 trending. When it comes to taking care of cancer  
21 patients, a lot of that is done as outpatient here  
22 in the United States. But as I've had the

1 opportunity to be a visiting professor and practice  
2 all over the world, it is quite a big difference  
3 between country to country. And even within the  
4 different countries, there's a difference in -- I  
5 just came back from a month in Italy, three  
6 different universities. There's a difference in  
7 the northern Italian versus southern Italian way  
8 that they take care of cancer patients.

9           So there are a lot of differences when it  
10 comes to managing these patients, and that can lead  
11 to the difference in heterogenicities related to  
12 the use of various projects.

13           Now, I mentioned that we do use multimodal  
14 treatment therapies. The problem with breakthrough  
15 cancer pain is that it happens so fast, usually,  
16 and it's such a high amount of pain. The intensity  
17 so hard, there aren't many things that you can use  
18 from a non-pharmacological standpoint to manage  
19 that.

20           In Xi'an [ph] China, they do try  
21 acupuncture. Some individuals are able to apply  
22 that on their own. But the universality of that is

1 quite limited. That's why it makes these products  
2 very unique for this very unique special patient  
3 population.

4 DR. BATEMAN: Thank you. Dr. Fry?

5 DR. FRY: You guys had talked earlier about  
6 your plan to propose changes, and it sounds like  
7 you accept the PPAF forms, both electronically and  
8 VFX, and there seems to be a lag time in that. You  
9 wait up to 7 days possibly for the fax and when the  
10 script's filled.

11 Is there any way to promote it more like  
12 some of the other REMS programs, like the  
13 isotretinoin or Clozaril, where it's more real  
14 time. I can't fill a Clozaril prescription without  
15 a yes right away, which validates the prescriber.  
16 I have to validate blood work. Is there a way to  
17 do that would maybe hopefully catch some of these  
18 ones that are sliding by?

19 MR. SHERMAN: Amanda?

20 MS. BULKLEY: I just want to clarify that  
21 the PPAF is completed real time on the Web, but if  
22 it's faxed in, it's processed within 24 hours.

1       There's not a 7-day lag time for that. But then  
2       I'll let you speak to any other comments you have.

3               MR. SHERMAN: I've got nothing for you.  
4       Sorry.

5               DR. FRY: No worries. Thank you.

6               MR. SHERMAN: While I'm here, can I clarify  
7       something?

8               DR. BATEMAN: Sure. Go ahead.

9               MR. SHERMAN: Thanks. Dr. Habel, when you  
10       asked why the Medicare data that Dr. Fleischman  
11       presented was so different than the prescription  
12       trend that you saw from the FDA and from us, if you  
13       look at the years, Dr. Fleischman's data I believe  
14       ended at 2014. If you carry that out, if he went  
15       out to the end of 2017, I think you would see the  
16       same decline.

17              DR. HABEL: [Inaudible - off mic].

18              MR. SHERMAN: I know.

19              DR. HABEL: [Inaudible - off mic].

20              DR. BATEMAN: Use the microphone, please.

21              DR. HABEL: The pattern, though, at  
22       least -- I don't have the slide in front of me.

1 But the FDA utilization and maybe the utilization  
2 data that you looked at, you're right that there  
3 was a flattening around 2012 through 2014, and then  
4 it drops again. But I thought that the Medicare  
5 data actually shows an uptick.

6 MR. SHERMAN: Well, I'm sorry. I didn't  
7 memorize the FDA's data, but I did memorize our  
8 data. If you look at our data, 2013, 2014 -- 2013,  
9 '14 and '15 -- there's a slight apex at 2015, but  
10 then 2016 and 2017 fall off cliffs.

11 DR. BATEMAN: Dr. Warner?

12 DR. WARNER: Thanks. I wanted to go back to  
13 the question about the cause of death from Dr.  
14 Stem --

15 MR. SHERMAN: Stemhagen.

16 DR. WARNER: -- Stemhagen. Thank you. It's  
17 such an important outcome for this population, and  
18 I think Dr. Dart alluded to the fact that the  
19 poison control center is known to underestimate  
20 death, particularly because I think with these  
21 types of deaths, they would happen very quickly or  
22 at least not in a hospital -- the person would

1       never get to a hospital or have any healthcare  
2       before their death. So it wouldn't necessarily end  
3       up in a system like the poison control center.  
4       Overall, I think 75 percent of drug overdose deaths  
5       never enter a healthcare system before their death.

6               But my question is you have very, very  
7       little data on the death. You just note that the  
8       death occurred. I guess you have some information  
9       about hospice. Do you have age or anything else  
10      you can look at? Presumably, many of these  
11      patients would have died of cancer. And if you  
12      don't, I think somebody from the FDA mentioned  
13      possibly other ways to capture that information.  
14      Have you thought about changing a form, adverse  
15      event, spontaneous event reporting?

16             DR. STEMHAGEN: The spontaneous adverse  
17      events use the MedWatch form, so they do have items  
18      there for that information. The difficulty is  
19      getting that information. Sometimes it comes in  
20      and the reporter just doesn't want to provide it,  
21      especially in certain sensitive kinds of cases.

22             One of the things that we are trying to look

1 at, and we're just starting to evaluate, is whether  
2 there's any way to use the National Death Index at  
3 all. Now, some of the deaths may be people for  
4 whom it's not prescribed, so that might not help.  
5 But we're looking at it from the standpoint of  
6 whether the REMS data could be used for that,  
7 whether we need to have IRB approval and how that  
8 would work with the National Death Index.

9 So we are trying to find other ways to see  
10 if we can supplement the data to try to be more  
11 complete.

12 DR. WARNER: Yes, it seems like that would  
13 be something that would be really valuable because  
14 the National Death Index does had the cause of  
15 death. So you may not know as much detail as you'd  
16 like, but you could know, in fact, the person died  
17 of cancer.

18 DR. BATEMAN: We have a lot of discussion  
19 questions to get through today, so we'll do one  
20 more question from Dr. Nelson, and then we'll move  
21 on to the charge to the committee.

22 DR. NELSON: Thanks. Maybe mine will be



1 quick and easy, hopefully. It's actually two  
2 questions, but they're both probably quick and  
3 easy.

4 For Dr. Radin, if I can go back to the FDA,  
5 if that's okay. The only thing we've really seen  
6 today that looks at the patient's perspective is  
7 some of the social media stuff that you talked  
8 about. I had done some social media research, and  
9 I realized you can get a lot of information. It's  
10 very hard to interpret, and there's a little  
11 natural language processing that goes on there and  
12 stuff like that.

13 But you seem to really look at counterfeit  
14 TIRF, and I'm wondering in that, there's a lot of  
15 other data out there about abuse, and how you score  
16 drug, and a lot of these other things. Did you  
17 look at any of that? And as a corollary to that,  
18 did you only limit yourself to social media? Did  
19 you look at conventional media?

20 There's been a lot of discussion nowadays  
21 about aberrant prescribing practices and a lot of  
22 lethal overdoses in people who ostensibly shouldn't

1       have otherwise died. Was there any ability to look  
2       at any of that?

3               DR. RADIN: The types of themes that we  
4       looked at were people who abused drugs, describing  
5       the high from various drugs, how to enhance the  
6       high, how to avoid overdose. That was the content  
7       or the general theme of a lot of these postings.  
8       There was minimal mention of aberrant prescribing.

9               The other thing is that -- I want to talk  
10       about -- we went into the social media search  
11       because we wanted to see if there was abuse  
12       happening of perhaps counterfeit TIRF medicines  
13       that were then being reported coming up in  
14       treatment center or poison center data; so just  
15       looking for some other explanation at what we were  
16       seeing to confirm or refute our findings in other  
17       data sources.

18               So you understand, it's difficult to make  
19       conclusions based on a qualitative analysis of a  
20       social media search, and that's why it kept our  
21       conclusions very general on that.

22               DR. NELSON: Fair enough.

1 DR. RADIN: Does that answer your question?

2 DR. NELSON: Yes. There's a lot of data out  
3 there --

4 DR RADIN: There is.

5 DR. NELSON: -- when you start looking at  
6 this stuff, and it is hard to interpret, I will  
7 tell you, because we looked at this about people  
8 looking to -- what their comments were about, for  
9 example, oxycodone. And they said, went to the  
10 dentist, got some oxycodone, feel really good now.  
11 Right? It could be they had dental pain and they  
12 feel good or it could be they got some drug from  
13 their doctor, from their dentist. So it's very  
14 hard to understand some of these things.

15 Can I just ask Judy or Sharon a question?  
16 What is your expectation when a physician signs the  
17 PPAF? When they say they understand that this is  
18 indicated only for cancer pain, is the expectation  
19 of the FDA that they're only giving it to people  
20 with cancer and that any other prescribing -- even  
21 though you're allowed to off-label prescribe, you  
22 don't normally sign a piece of paper that says

1 something like this, when I give you amoxicillin  
2 for some non-ear ache, for some different  
3 indication. But here, I'm doing something that I'm  
4 signing my name to that sort of implies something.

5 Is there an expectation?

6 DR. HERTZ: The primary expectation, what we  
7 were hoping to achieve was not necessarily to  
8 restrict off label indication but to avoid opioid  
9 non-tolerant patients being prescribed this drug.  
10 So back when we started this REMS, this was brand  
11 new, and this was an incredibly closed system that  
12 we were developing for this.

13 We had no data or experience to base this  
14 sort of thing on, so we came up with a system, and  
15 then we got some feedback. And the initial  
16 feedback was that physicians found it somewhat  
17 burdensome, and that's anecdotal. And then changes  
18 were made. The attestation was changed. It was a  
19 little bit less absolute, and that was in response  
20 to prescribers.

21 So we've been trying to follow the outcomes  
22 with all of this, but it's been difficult because

1 of all the data challenges that we've been talking  
2 about. The intent of the REMS was to restrict use  
3 of these products to opioid-tolerant patients, not  
4 necessarily with cancer.

5 DR. BATEMAN: We'll now proceed with the  
6 charge to the committee from Dr. Manzo

7 **Charge to the Committee - Claudia Manzo**

8 DR. MANZO: Thank you. So you've heard  
9 presentations today about the TIRF medicines,  
10 including the risks of these products, as well as  
11 their place in the treatment of breakthrough cancer  
12 pain. You have also heard about the TIRF REMS,  
13 including the goals, the requirements, and how the  
14 shared system REMS has been implemented by the  
15 sponsors.

16 Finally, you've heard the sponsors, FDA, and  
17 the invited speakers discuss analyses of multiple  
18 data sources to determine if the REMS is meeting  
19 its intended goals and objectives.

20 Based on the available data. the TIRF REMS  
21 program appears to have been implemented as  
22 intended to ensure that prescribers and pharmacists

1 receive training on the risks and the safe use of  
2 TIRF medicines prior to prescribing and dispensing,  
3 and to ensure that patients are informed about the  
4 risks and the safe use of TIRF medicines before  
5 taking them.

6 However, the operational aspects of the  
7 program do not inform medical outcomes that concern  
8 us most. One of our principle concerns from the  
9 assessment is the finding, based upon claims data,  
10 that a substantial proportion of patients  
11 prescribed TIRF products are not opioid tolerant.  
12 FDA has independently conducted a validation of the  
13 methods used in these kinds of claims studies to  
14 make sure the finding is real.

15 Dr. Jeffery's work, which you heard today,  
16 suggests that it is. We have asked the sponsors to  
17 conduct a validation study to reproduce this  
18 finding. We have also looked at our own FAERS  
19 database for adverse events to see whether we have  
20 reports of serious adverse events or deaths among  
21 opioid non-tolerant patients who were administered  
22 TIRF products. But as you heard, the reports are

1 not detailed enough to inform this issue, so we  
2 have asked the sponsors to conduct a study to look  
3 at outcomes of patients prescribed TIRF products  
4 who are not opioid tolerant, and these studies are  
5 ongoing.

6 There have been a significant decline in  
7 prescribing of TIRF products since 2010, and TIRF  
8 products are only currently prescribed to  
9 approximately 5,000 patients nationwide. This  
10 further challenges the conclusions that can be  
11 drawn from the limited surveillance data and  
12 affects our ability to evaluate the effectiveness  
13 of the REMS.

14 So we've been asking committees to discuss  
15 the following: whether the plan validation of a  
16 claims space algorithm is likely to provide  
17 information to determine the extent of use in  
18 opioid-tolerant patients; if linked claims outcome  
19 studies are likely to be informative to compare  
20 rates of overdose in opioid non-tolerant patients  
21 to opioid-tolerant patients.

22 The best approach is to estimate the number

1 of inappropriate conversions between TIRF products  
2 and the extent or the accidental exposure to  
3 children and others for whom TIRF products are not  
4 prescribed.

5 We'll be asking whether the prescriber,  
6 patient, and pharmacy surveys sufficiently inform  
7 whether these stakeholders understand the risks and  
8 safe use of these products and why there might be a  
9 disconnect between what they know and how they  
10 prescribe these products.

11 We'll ask you to discuss the significance of  
12 finding suggestive of increased rates of adverse  
13 events despite decreasing use of TIRF products; the  
14 factors that resulted in the decreased use of TIRF  
15 products; and whether the goals and objectives are  
16 still appropriate given the limitations of the  
17 data; and if you believe the goals and objectives  
18 are appropriate, whether the TIRF is adequately  
19 designed to meet those goals and objectives.

20 We want to thank you, again, for your time  
21 and commitment in helping us with these really  
22 important questions. Thank you.



**Questions to the Committee and Discussion**

DR. BATEMAN: Thank you.

We will now proceed with questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

There are four discussion questions, and each of them have multiple parts, so we'll divide them up as we go. Starting with discussion question 1, the intent of the transmucosal, immediate-release fentanyl TIRF risk evaluation and mitigation strategy, REMS, is to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors. And then there were four objectives, and let's take each of them in turn.

Objective 1, ensuring prescribing and dispensing TIRFs only to appropriate patients, e.g., opioid-tolerant patients, discuss whether the following strategies will inform if this objective

1 is being met, 1, further validation of claims-based  
2 algorithms through EMR and chart study; and 2,  
3 linked claims-based outcome studies in patients  
4 prescribed TIRF medications comparing opioid  
5 non-tolerant patients to tolerant patients. And  
6 then discuss the other strategies that the TIRF  
7 REMS industry group should undertake to inform the  
8 objective.

9 So perhaps for part A, people can comment on  
10 the studies that have been proposed and any  
11 specific considerations that you think are  
12 important in terms of the design and conduct of  
13 those studies.

14 Dr. Meisel?

15 DR. MEISEL: Steve Meisel, Fairview,  
16 Minneapolis. First of all, just as an overriding  
17 comment, I'm not sure any of the data today answers  
18 a key question -- and the question is why am I  
19 getting feedback?

20 (Laughter.)

21 DR. MEISEL: No. We're assuming that all of  
22 these TIRFs behave the same, and I'm not sure

1       that's a valid assumption. Sixty percent of the use  
2       of these drugs today are with a drug that didn't  
3       exist at the time the REMS came about, and that's  
4       Subsys.

5               So to me, it's hard to differentiate and to  
6       tease out whether some of the problems we're  
7       talking about are related to the unique product and  
8       the issues with Subsys or are class effects,  
9       because if it's Subsys, then our approaches with  
10      that need to be different than they would be for  
11      the TIRF and the REMS as a class. And I don't  
12      think we have any data whatsoever that I've seen  
13      today that helps us to differentiate any of that  
14      sort of thing, and that's somewhat disappointing.

15             I think there's no doubt that we all  
16      understand that as new drugs come out, they get  
17      marketed in different ways. But we don't know to  
18      what extent the non-cancer use, the non-tolerant  
19      use, or any of these kinds of things, or the death  
20      rates or anything like that is higher, lower, or  
21      indifferent with Subsys. And I think that's going  
22      to sort of taint the rest of our conversation

1       today, just as a general observation here.

2               But with that in mind, everything that I see  
3       here in A, none of that helps us to mitigate the  
4       risk of misuse, abuse, addiction, overdose, or  
5       serious complications because it's all  
6       retrospective data review. If you want to reduce  
7       any of that stuff, we've got to be more proactive  
8       with that.

9               Some people have suggested today that we do  
10       more of a prior authorization approach where you  
11       actually intentionally ask the provider, or whoever  
12       is enrolling the patient into the program onto the  
13       drug, some intentional questions about prior  
14       narcotic use, the doses, and the diagnoses, and  
15       these sorts of things.

16              That would get us to be more likely to  
17       prescribe this drug to populations for whom it's  
18       intended. Everything else that's being proposed  
19       might be helpful for further data analysis later,  
20       but won't help us to inform how we're going to  
21       improve rates of misuse, overuse, abuse, addiction,  
22       and that sort of thing.

1 DR. BATEMAN: Dr. Brown?

2 DR. BROWN: Well, I have two comments. And  
3 one of them is that tolerant is an indirect way of  
4 evaluating the problem that one would have with  
5 this class of medications. And what we really  
6 should be thinking about is what's the outcome that  
7 tolerance is going to be focused on.

8 Tolerance, if a patient is tolerant and  
9 there's no adverse outcome, then there's no  
10 problem. If there's an adverse outcome associated  
11 with tolerance -- and I'm presuming that in the  
12 initial run-up to marketing these drugs, there was  
13 discern that tolerance or lack thereof was going to  
14 be a problem. And pharmacokinetically, one would  
15 believe that there is.

16 But I think we've answered, we've walked all  
17 around the question of tolerance today, and I'm not  
18 sure in what way we can provide more information  
19 relating to that. But I do think we need to  
20 provide more information concerning the outcome.  
21 That would be a respiratory arrest, emergency  
22 department admissions, and death. Those are hard

1 outcomes that we should be looking at.

2 The second comment I have really focuses on  
3 what Dr. Meisel has been saying. And that is that  
4 if we have one brand drug that is driving the rest  
5 of the information that we are looking at, then we  
6 should look at that one brand drug. It's apparent  
7 to me that over the course of the last five years,  
8 there's been a substantial increase in the  
9 marketing of one branded drug, and concurrent with  
10 that, the FAERS data demonstrates that there's been  
11 a rise in the number of deaths.

12 The question is, is the rise in the number  
13 of deaths arithmetically related to the rise in the  
14 number of prescriptions for that particular drug or  
15 not. But before we go and expend a lot more  
16 resources around the general questions, I think we  
17 really have to answer that specific question.

18 DR. BATEMAN: Dr. Litman?

19 DR. LITMAN: Thank you. Ron Litman. I also  
20 want to make a couple of comments, first of all,  
21 about tolerance, to echo what my colleagues also  
22 said. The tolerance, the burden would be on the

1 physician to determine who's tolerant in order to  
2 prescribe, and the pharmacist to determine who is  
3 tolerant in order to administer to. So it's just  
4 essentially impossible.

5           You could look at electronic databases like  
6 the PDMP or something that would be equally as  
7 useful if such a thing exists. And even if you  
8 thought the patient was tolerant or wasn't, you  
9 don't know what the patient is actually ingesting.  
10 And asking the patient I don't believe would be  
11 accurate.

12           The FDA has asked the TRIG to conduct  
13 studies that attempt to determine whether or not  
14 complications are more or less likely in  
15 non-tolerant versus tolerant patients. But without  
16 independent oversight, I can't imagine that we  
17 would get accurate results. And with the patient,  
18 you could ask them and you could provide education.  
19 But just everything we've heard here today, it's  
20 hard to believe that it could be accurate. And  
21 I'll save other comments for the other questions.  
22 Thank you.

1 DR. BATEMAN: Dr. Kulldorff?

2 DR. KULLDORFF: Martin Kulldorff. A key  
3 question I think is -- I alluded to this  
4 before -- the people who are getting this drug, are  
5 they getting it because it's indicated for them or  
6 not? So it's very clear that for a cancer patient  
7 with breakthrough pain, this is a very, very  
8 important drug they need. At the same time, I  
9 haven't seen any evidence at all that this is a  
10 useful drug for non-cancer patients, and there's  
11 evidence that -- and the safety data I think is  
12 very uncertain or very difficult to do anything  
13 about.

14 So I think we're basically ignorant about  
15 the safety profile, so therefore, I think it's a  
16 little dangerous to give this where it's not  
17 indicated.

18 In terms of getting more data, I think the  
19 data that we have from Optum and from the CMS I  
20 think is very good data. If we look at that as  
21 well as the other data, it's clear that about 20 to  
22 42 percent -- the numbers are a little different



1 from different ones -- are opium non-tolerant, and  
2 that about 72 percent do not have cancer. There's  
3 less information about the cancer than the other  
4 one.

5 We can get better numbers. It will be good  
6 to get slightly better numbers. But if we assume  
7 independence, then we find that about 16 to 22  
8 percent of people who get these drugs are actually  
9 getting it because it's indicated for cancer in  
10 opioid-tolerant people, while 78 to 84 percent get  
11 it for something for which this is not indicated.

12 So based on those numbers -- and they could  
13 be off a little bit because it was sort of napkin  
14 calculations instead of statistician. Even if  
15 they're off a little bit, it's pretty clear that  
16 the REMS program is not functioning in terms of  
17 preventing people to get this for which it's not  
18 indicated.

19 That doesn't mean that the REMS program is  
20 implemented in a right way because I was very  
21 impressed with all the steps of implementing the  
22 thing that was designed. I think it's more of a

1 question of how it was designed. It could actually  
2 be that it's also preventing many cancer patients  
3 from getting it because it's too burdensome for  
4 many people, and at the same time slipping many  
5 through the cracks.

6 One of the things that the TRIG group  
7 proposed was to have the PPAF revision to add  
8 prescriber attestation that patients are opioid  
9 tolerant. I think that might be much more  
10 efficient, in my guess, than many of the  
11 educational programs. And I think one could also  
12 add that they have to be at least 18 years old and  
13 that they need to have cancer.

14 I heard that there are, of course, some  
15 people who think -- there were some sort of  
16 arguments that off-label use is okay. I guess I  
17 take a more pessimistic view. For most drugs, I  
18 think off-label use is okay, but for opioids, I  
19 think we should be very, very careful with  
20 off-label use because there is such a strong  
21 incentive for many people who want it for  
22 non-medical reasons.

1           So to have a REMS statement that the  
2       prescriber will attest to, both to being opioid  
3       tolerant as well as having cancer, I think might be  
4       a good way to reduce the use in people for which  
5       it's not indicated. At the same time, if you  
6       remove some of the other requirements of lengthy  
7       education, so filling in forms and signing things  
8       that most people might not even read, I think you  
9       might actually lower the burden for the cancer  
10      patients who actually need this drug to manage the  
11      breakthrough pain.

12           In summary, I think that more data is  
13      probably not needed. I think some additional  
14      analysis on the excellent Optum and CMS data will  
15      be useful to get more precise estimates of who gets  
16      this drug and who does not; useful and not very  
17      costly or burdensome. But my recommendation would  
18      otherwise be to  
19      revise the REMS program to make attestations as  
20      [indiscernible] education. Thank you.

21           DR. BATEMAN: Dr. Nelson?

22           DR. NELSON: Thanks. Lewis Nelson from

1 Rutgers. I've always suggested that education's an  
2 important thing, but it's never the solution. And  
3 I think we do have to make sure that everybody is  
4 educated to a certain extent, and we spend a lot of  
5 time in our REMS creating educational programs. I  
6 think they usually do fall short, and we wind up  
7 having to go beyond that.

8 What always amazed me about this -- and I'll  
9 go back to buprenorphine for a second -- is that it  
10 takes 8 hours to get certified on buprenorphine  
11 administration, which is a benign drug, which is  
12 pretty hard to overdose and hurt yourself on. And  
13 it takes 30 minutes to get trained and certified to  
14 give out this drug. It does seem like somewhat of  
15 a paradox.

16 In addition, even with that education, it  
17 sounds like people don't remember what they  
18 learned. And if we're using 80 percent as the bar,  
19 and we're not even hitting that bar for getting the  
20 questions right and understanding how this should  
21 be prescribed, I think we're really doing our  
22 patients a big disservice.

1           You can't imagine asking a doctor where the  
2   liver is and only having a 80 percent chance of  
3   getting it right. When you're giving out a drug  
4   that this dangerous, I think you should have to  
5   have 100 percent across the board on everything.  
6   This is not buprenorphine. This is unbelievably  
7   dangerous in comparison. And to have such a low  
8   standard seems pretty unacceptable to me.

9           We saw from some of the data we were shown  
10   earlier that as an initial dose, some patients were  
11   getting a thousand micrograms, or 800 micrograms.  
12   That's a whopping dose regardless of which  
13   formulation you're using. So clearly, there's a  
14   lot of misunderstanding there. Nobody should get  
15   that as an initial dose. Maybe they'll titrate up  
16   to that, but that should never be an initial dose.

17          I do think, per your comment, Sharon, about  
18   what the intent was of writing in that this is for  
19   cancer pain, if we didn't mean that, we shouldn't  
20   have included it, but we did include it as an  
21   indication. I realize we don't have  
22   contraindications are not having cancer pain, but

1       it implies to me that's what we wanted there to be.

2               As per some of the earlier comments, I fully  
3       agree that cancer pain, especially this sort of  
4       cancer pain, has a certain life expectancy  
5       associated with it, a sort of end-of-life  
6       palliative care, very different than chronic  
7       non-cancer pain where people live 40 or 50 years.  
8       You are dealing with tolerance in and hyperalgesia,  
9       and a lot of other things, abuse, that go along  
10      with it that we're not very concerned about in  
11      end-of-life care.

12              So I really do very much disentangle those  
13      two groups and feel that we have to really hone in  
14      on the indication. And if we have to write  
15      non-cancer as a contraindication, then maybe that's  
16      something we ought to do because it seems very  
17      important.

18              My last comment is ways to make this  
19      better -- and I know FDA hates the R word, the R  
20      word being registry. It seems like with only 6,000  
21      patients, this is not an unreasonable size. I know  
22      we once talked about the extended-release opioids,

1       300 million patients that take that. But here with  
2       6,000 patients, I don't see why we couldn't -- it's  
3       almost equivalent to a prior authorization in a way  
4       where you need to make sure that we're giving this  
5       only to the people that need it and should be  
6       getting it, and we're not giving it to other  
7       people.

8               My comments before about conventional media,  
9       you can't almost open up the newspaper where I'm  
10      from, New Jersey, and not read about a doctor who's  
11      going to jail or being brought up on criminal or  
12      civil charges for misprescribing a TIRF opioid. So  
13      I think there are a lot of problems out there, and  
14      the only way we're probably going to rein it in is  
15      to take away some of our ability to prescribe it.  
16      There's a lot of politics and philosophy in there,  
17      I realized, but to answer B on the objective, I  
18      think we need to have more control and not less.  
19      And I could see this living up to like a  
20      thalidomide level of concern, where we really want  
21      to make sure that only people that deserve this  
22      drug, that should be getting this drug are getting

1       it.  Thanks.

2               DR. BATEMAN:  Thank you.  I also want to  
3       make sure we touch on part A, and that is  
4       discussion of the validation of the claims-based  
5       algorithms for assessing whether patients with a  
6       non-tolerance are getting the medication.  We heard  
7       a presentation regarding the Optum data where there  
8       was a lot of leakage and they weren't able to do a  
9       really rigorous evaluation of that question using  
10      those data.

11              So for people that have experience with  
12      these kinds of data, what are some of the design  
13      elements that could be incorporated?  I think  
14      there's also a presentation or a suggestion from  
15      the sponsors that they're going to do a study  
16      within the Henry Ford Health Care system.  What  
17      should be the design elements that are included in  
18      that study to ensure that valid data are obtained?

19              Dr. Warner?

20              DR. WARNER:  I was actually going to comment  
21      about that.  Being a researcher, I do always  
22      appreciate more research.  But I do think that it's



1       worth considering doing for the validation studies,  
2       particularly since I learned that the EMMR study  
3       that was already done that Dr. Jeffery presented  
4       was based on EHRs from as early as 2007, where  
5       there was much less information in those EHRs.

6               So I think it's worth considering doing  
7       another validation study, particularly one where  
8       they could read the notes and have more of those  
9       continuing care documents available. So it may be  
10      that they'd have to wait to do that study a year or  
11      two, but I imagine by the time a study would be  
12      able to be suggested. I guess the TRIG group is  
13      going to be doing that as you said. But I endorse  
14      the idea of looking at a further validation study.

15             DR. BATEMAN: Any other comments on the  
16      design of the EHR validation study?

17             (No response.)

18             DR. BATEMAN: And what about part 2? The  
19      linked claims-based outcome studies trying to  
20      assess what the risk is of prescribing these  
21      medications in non-tolerant patients, any design  
22      considerations that should go into those studies?

1           Maybe we can collect some comments on the  
2           question I just raised, and then we'll continue to  
3           go around. Anyone have any specific comments on  
4           part A2?

5           DR. WARNER: I had a question about that.  
6           What was the outcome that they were going to be  
7           using to look at -- there's a claims-based outcome  
8           study, so what's the outcome? Is it --

9           DR. STAFFA: This is Judy Staffa. We had  
10          asked them to look at fatal and non-fatal overdose.

11          DR. WARNER: Okay. I think that would be  
12          very useful.

13          DR. BATEMAN: Dr. Warholak?

14          DR. WARHOLAK: So thinking of that, then,  
15          Dr. Goudra gave me an idea while he was asking his  
16          question. If we're looking for the fatal events,  
17          those are obviously going to be fairly rare. And  
18          one of the problems we've had in a lot of the data  
19          that we've been shown today is that we have really  
20          small numbers. And in looking at slide CC-26,  
21          obviously Western Europe doesn't have that issue.

22          So might it be worthwhile to begin to

1       investigate this issue in Western Europe and some  
2       of their data to see how small the signal really is  
3       before we try to come here in a much, much smaller  
4       population and identify that?

5               DR. BATEMAN: Dr. Warner?

6               DR. WARNER: I had a comment about that.  
7       563 patients out of 6,000 is not terrifically rare.  
8       Somehow we're missing some of the people who are  
9       dying in these analyses. Unless I'm interpreting  
10      what I've seen --

11              DR. STAFFA: Yes. I think the 500-ish  
12      number is from spontaneous reports. And remember,  
13      that kind of narrows that down. There's no  
14      requirement for there to be a causal connection.

15              DR. WARNER: Well, yes.

16              DR. STAFFA: And they could be other kinds  
17      of fentanyl.

18              DR. WARNER: And other kinds of fentanyl.

19              DR. STAFFA: So I think that's the broadest  
20      picture.

21              DR. WARNER: Okay. Sorry. I misunderstood  
22      the --

1 DR. BATEMAN: Dr. Brand?

2 DR. BRAND: Yes. As far as the number of  
3 deaths -- and I agree with you, there is at least  
4 enough to look at. I guess my concern is how many  
5 physicians are willing to put the cause of death.  
6 It's kind of a gray area. If you're giving them a  
7 drug to basically alleviate pain oftentimes at the  
8 end of life, is it the drug or is it the cancer  
9 that's causing it, how many prescribers in our  
10 current legal environment are willing to put that  
11 as a cause of death?

12 DR. WARNER: I actually was speaking of fact  
13 of death, the fact that the patient died. Cause of  
14 death I think would be very nice to know as well.

15 DR. BATEMAN: Dr. Sandbrink?

16 DR. SANDBRINK: Friedhelm Sandbrink,  
17 Washington, DC VA. I would really like to see more  
18 evidence and information from the PDMPs. Those are  
19 mandated reporting by any provider and  
20 pharmacy -- or pharmacy I should say -- pretty much  
21 in any state. And I think we have a data set here  
22 that is universally now implemented with very few

1 exceptions in the United States. It has all the  
2 data going back to any opioid prescribing in some  
3 states quite a while. And I think you could use  
4 that obviously for any new start of TIRF  
5 medications and find out the PDMP data, as well as  
6 anybody who had a negative outcome on these meds,  
7 and see, really, what's the trajectory of their  
8 prescribing?

9 So if you can get access to the PDMP data, I  
10 understand each state has their own one. Patients  
11 might get a prescriptions from a different state,  
12 but with PDMP and PDMP Connect, we do have data  
13 across states now, and I would like to encourage  
14 that.

15 DR. BATEMAN: Dr. Katzman?

16 DR. KATZMAN: I'll just mention a couple  
17 things that I was just talking with Dr. Brand  
18 about. There's over a million new cases of cancer  
19 per year. Let me get to the actual statistics.  
20 There's about 600,000 people who die every year of  
21 cancer, yet there's about 4,700 patients who are  
22 getting TIRF meds a year. So that means, on one

1 hand, there's probably an undertreatment of pain,  
2 acute pain, for patients with cancer. Yet on the  
3 other hand, 79 percent of patients getting TIRF  
4 meds do not have cancer.

5 So there's a huge disconnect going on right  
6 now with an undertreatment of patients who probably  
7 need cancer pain meds, and then an overtreatment of  
8 patients getting opioids, really, really potent  
9 opioids, who probably don't need them. That's my  
10 first thing that I'll mention.

11 Then I highly, highly agree with Dr. Meisel  
12 and Dr. Nelson that we need to be much more  
13 proactive on the educational front like we've done  
14 with most states who now have CME requirements in  
15 pain and safe opioid prescribing like we did with  
16 the CDC pain management guidelines for chronic  
17 non-cancer pain, where we recommended that we start  
18 with immediate-release opioids before going to  
19 long-acting opioids, which is ironically just the  
20 opposite here. I think we can do a lot more on the  
21 educational realm.

22 The last thing that I'll mention is that

1 Doris Auth said in her statement, was that of the  
2 prescribers who are giving TIRF meds, 7 percent are  
3 oncologists and 15 percent are NPs or PAs. That  
4 means only 22 percent of the clinicians prescribing  
5 TIRF meds, if you add the NPs and PAs, are actually  
6 oncologists or mid-level providers, meaning the  
7 rest are not in the oncology realm. And I'm being  
8 overly inclusive by adding the mid-level group.

9 So if we're really wanting to hone in and  
10 get these medicines to the patients who it's really  
11 designed for, meaning the patients with acute  
12 cancer pain, we need to do a much better job of  
13 educating oncologists and mid-level providers  
14 working in the cancer field that this is how it's  
15 used. Thank you.

16 DR. BATEMAN: Dr. Arfken?

17 DR. ARFKEN: Cynthia Arfken, Wayne State  
18 University. I want to echo many of the other  
19 comments. I feel that we need to look at all  
20 deaths, not just fatal overdoses, including like  
21 what other drugs are using. And if the registry is  
22 the best way, if there's no other way of doing a

1 cohort, then I think it needs to be done that way.

2 I'm also concerned about the access to  
3 treatment. One of the things is the prescriptions  
4 went down prior to the implementation of the REMS,  
5 but it seems like compared to the Europe data, that  
6 it's completely undertreated here in the United  
7 States.

8 DR. BATEMAN: Great. And we're going to  
9 have more time to talk about the access later.  
10 Dr. Joniak-Grant?

11 DR. JONIAK-GRANT: Elizabeth Joniak-Grant.  
12 Two quick comments. Dr. Nelson had mentioned the  
13 possibility of a registry. One thing I think we'd  
14 have to be mindful of with that is that's really  
15 scary to patients. Whenever there's talk of  
16 registries or they feel they're being tracked, they  
17 get very nervous. They worry about that -- it's  
18 basically to have law enforcement eventually come  
19 into their lives. They get very concerned about  
20 it. They get concerned that their meds are going  
21 to be taken away. They get concerned how that  
22 information is going to be used. So if we're



1       talking about something with a registry, it has to  
2       be handled very, very carefully.

3               Also, I think we have to be mindful that  
4       before we go forward and say, oh, this shouldn't go  
5       to non-cancer pain patients, first we need to know  
6       what are the diagnoses of the people who are  
7       getting it for non-cancer pain because there are  
8       other types of illnesses and things that have  
9       breakthrough pain. And I think it's important for  
10      us to see is it just a few things that it's being  
11      used for off label? Is it a multitude of things?  
12      But I feel that we kind of need to know how it's  
13      being used off label before we say, oh no, no, no,  
14      it shouldn't be used off label.

15             DR. BATEMAN: A few members of the committee  
16      made the suggestion that the PPAF should be  
17      strengthened to include an indication, not just  
18      that the patient's opioid tolerant, but that they  
19      have cancer pain. And I'm wondering if some of the  
20      other folks on the committee can weigh in on that.  
21      Is that something that the FDA should entertain,  
22      requiring not just that the patients be opioid

1       tolerant but have cancer pain and evaluating the  
2       risks-benefits of the medication?

3               Dr. Litman?

4               DR. LITMAN: Thank you. Ron Litman. I  
5       understand where that may have originally come  
6       from, that some of the original studies were done  
7       on cancer pain, but to me, it always seemed a  
8       little bit odd that we would say that only  
9       cancer-pain patients are deserved of this drug that  
10      can take away acute pain quickly. And there are  
11      certainly other kinds of patients that have spikes  
12      in severe pain. Obviously, the goal long term is  
13      to get people off opioids. I would never argue  
14      with that. But it's an awful situation when you  
15      have pain and you need something quickly.

16              I hear a lot of talk about restricting it to  
17      people with certain kinds of pain, but I really  
18      have a hard time ethically and morally to restrict  
19      it to only -- saying that there's only one kind of  
20      person that is deserved of this kind of pain  
21      relief. That's my feelings.

22              DR. BATEMAN: Dr. Sandbrink?

1 DR. SANDBRINK: Friedhelm Sandbrink,  
2 Washington, DC. I want to echo that to some  
3 degree, that I would have concerns if suddenly this  
4 PPAF gets changed that it has to be cancer. I feel  
5 that we have to realize that it seems to be that  
6 the majority of prescribing possibly, according to  
7 CMS data, is in non-cancer patients. We don't know  
8 what kind of patients these are.

9 If there was suddenly the requirement that  
10 it's only for cancer, some of these patients, who  
11 possibly are very, very tolerant by now and  
12 certainly significantly used to taking this  
13 medication, to take this away, suddenly  
14 away -- that's what it would mean -- would  
15 potentially really jeopardize their care.

16 I think a clarification that we have to do  
17 is, really, in regard to new starts, I think that's  
18 something that if you want to talk about providing  
19 better guidance to prescribers that this should not  
20 be started in a non-cancer patient, if that's even  
21 something we'd go to, that maybe is more of a  
22 consideration. But taking these patients who have

1        maybe non-cancer pain, who've gotten really used to  
2        this medication, while these are very high-dose  
3        opioid tolerant and maybe have significant  
4        restrictions in taking any medication by mouth, I  
5        think I would be greatly concerned about taking  
6        medications away that has been part of their care  
7        plan, and leaves them basically without anything  
8        that is similar to that to substitute with.

9                DR. BATEMAN: Thank you. Dr. Brown?

10               DR. BROWN: Well, I would have to agree  
11               completely with you that you really can't be taking  
12               drugs away from patients. But I will say this.  
13               We're in the middle of a national conversation now  
14               about the use of long-lasting opioids in chronic  
15               pain. So when you are in the middle of that  
16               conversation, you are dealing with an issue of  
17               efficacy versus risk.

18               For patients that have cancer, especially if  
19               it's end-of-life care, the efficacy versus risk  
20               equation balances on one side, but for patients  
21               where there's a real question in many people's  
22               minds about whether the efficacy of the drug is

1       going to be efficacious at all, whether it's going  
2       to be efficacious for a short period of time but we  
3       know that the risk is going to be great, then I  
4       think you have to ask questions about whether or  
5       not we need to ask more questions about the use of  
6       it in non-cancer pain for new patients.

7               DR. BATEMAN: Dr. Meisel?

8               DR. MEISEL: I am very sensitive to  
9       obviously don't take suddenly people off of a  
10      medication that they're potentially dependent on.  
11      But I don't think that's really the question here.

12              The key problem that I see is that you've  
13      got a drug that was very narrowly designed, or a  
14      group of drugs that was very narrowly designed, for  
15      a very specific population and situation. And  
16      apparently, the use of it has morphed into all  
17      sorts of other things, and the dynamic of this  
18      conversation is tilting towards, well, I guess  
19      that's okay because people have found uses for it.

20              It seems to me that if a sponsor or a group  
21      of sponsors wants to make a case that their drug  
22      ought to be used for a broadened indication, then

1       they can come to this committee, or to the FDA  
2       anyway, with a proposal to expand the indication to  
3       include X, Y, and/or Z in different kinds of  
4       populations. So they can back that with rigor of  
5       science, looking at a safety, looking at efficacy,  
6       and balancing that out.

7               But it's not for us today to be sitting here  
8       and saying, well, I guess they're using it  
9       two-thirds of the time in situations that it wasn't  
10      designed, so let's figure out a way of enabling  
11      that. I think that's the wrong approach for a drug  
12      that is as potent and as potentially seriously  
13      damaging to individual patients, family members,  
14      and the community, as these are.

15             DR. BATEMAN: Dr. Joniak-Grant?

16             DR. JONIAK-GRANT: Elizabeth Joniak-Grant.  
17      I'm not sure with saying, when we were talking  
18      about the indications, if this is how it would be  
19      worded, but I think we have to also be careful  
20      about saying it is contraindicated, or using strong  
21      language that says this is for cancer pain; you  
22      really shouldn't be using it for non-cancer pain.

1           We have to be mindful as patients, then,  
2       reading the other warnings and saying, oh, and I'm  
3       supposed to be opioid tolerant, and I'm supposed to  
4       do this. But hey, I didn't have to do that other  
5       thing, so do these things even really apply?  
6       Because it does become that way sometimes with  
7       medications, and you call your doctors, and they  
8       say, oh, it's okay, you're fine in this.

9           So we have to be mindful of that tension  
10      that could go on when you're getting certain  
11      information and then you're getting other  
12      information.

13           DR. BATEMAN: Dr. Nelson?

14           DR. NELSON: Thanks. Lewis Nelson from  
15      Rutgers. I just wanted to weigh in on the  
16      conversation about using it off label. I tend to  
17      agree with Steve and Rae that while we can't just  
18      pull medications away from people, I think we have  
19      to be very cautious about broadening indications on  
20      things that we don't have good evidence for.

21           Clearly, we've gotten ourselves into a  
22      predicament today with opioids by lax prescribing

1 practices and relatively poor oversight. And I'm  
2 just concerned that we're broadening an indication  
3 a little bit too quickly. I like the idea that  
4 Steve put forth that this is a very narrowly  
5 designed drug. If there's an indication that it  
6 should be used for not chronic, non-cancer pain,  
7 not end-of-life care, then they should put some  
8 research together and show that, because I clearly  
9 get concerned about people, as I commented before,  
10 how we have to sort of differentiate the  
11 end-of-life care where a little bit too much drug  
12 has a lot less of an implication then in somebody  
13 who's going to live for the next 40 years.

14 We know that drugs that are rapid on/rapid  
15 off are associated with much greater euphoria and  
16 abuse, a higher risk of addiction, perhaps more  
17 hyperalgesia. And I think that before we know more  
18 about using these drugs, I would really try to  
19 limit it to what we know it might maybe work for.  
20 And I'm not even sure we have great data that it  
21 works for that. We didn't talk about efficacy in  
22 breakthrough pain here at all today.



1           Just to comfort the people that are at the  
2     table, I have no preconception that FDA would ever  
3     put a registry together for this. I just throw it  
4     out there to be provocative because I do think this  
5     is one of those drugs that sounds dangerous enough  
6     that it might rise to that standard. When you  
7     think about the drugs we've created registries for,  
8     this one seems to be dangerous enough, associated  
9     with enough aberrant prescribing and adverse  
10    outcomes, that we know exist, that it might rise to  
11    that level.

12           DR. BATEMAN: Dr. Goudra?

13           DR. GOUDRA: Basavana Goudra pain medicine.  
14    It looks like Dr. Meisel almost stole my talk, what  
15    I was thinking. It's kind of catch-22 for FDA. If  
16    you do approve for any non-cancer pain -- with the  
17    end [indiscernible], so it can just go anywhere.

18           But having said that, having suffered  
19    non-cancer pain myself, severe neck pain where it  
20    was unbelievable, 10 out of 10, but then it will go  
21    away, I think it's probably a good idea to approve  
22    it maybe with some restrictions, or in terms of

1 duration, or in terms of dosing for a non-cancer  
2 indication. That's what I think, and it's a  
3 dangerous territory to get into. Thank you.

4 DR. BATEMAN: Dr. Brand?

5 DR. BRAND: Just a quick comment on A and B,  
6 or A primarily, and discuss whether the strategies  
7 will inform if the objectives are being met. I'll  
8 go back to Dr. Meisel's earlier comment that, yes,  
9 it would be actually be good to get further  
10 claims-based data broken out maybe drug by drug by  
11 drug to see if there is problematic medications.

12 The second, where it says comparing opioid  
13 non-tolerant to opioid tolerant, I'd like to see  
14 data not just on deaths but just on which  
15 prescriptions are going to who because, if I'm not  
16 mistaken, it's contraindicated in non-tolerant  
17 patients. And as a pharmacist, contraindicated  
18 means that patient doesn't get it under any  
19 circumstances, and we know that a high amount of  
20 patients are. So I'd really like to see further  
21 data on that.

22 DR. BATEMAN: Before we conclude on this

1 section, we've discussed the idea of broadening the  
2 REMS to restrict the use of the medication to just  
3 patients that have cancer pain. And there's been  
4 clearly some disagreement on that question as well  
5 as the need for additional education.

6 Anything else that the TIRF REMS industry  
7 groups should be undertaking to inform that the  
8 medication goes to appropriate patients? Any other  
9 comments before we wrap up this section?

10 (No response.)

11 DR. BATEMAN: Okay. So just to summarize on  
12 Objective 1, I'll start with part B, strategies of  
13 the TIRF REMS industry group should undertake to  
14 inform if this objective -- as I mentioned, I think  
15 there was quite a big discussion about whether the  
16 REMS should be extended and the PPAF amended to  
17 require an attestation that patients have cancer  
18 pain, that patients be older than 18, and the  
19 patients be opioid tolerant.

20 There was disagreements amongst the members  
21 of the committee with respect to this point with  
22 some pointing out that there's utility for this

1 drug outside of cancer pain, that there are  
2 patients who are using this medication currently,  
3 and if the medication was withdrawn from them, that  
4 could be problematic.

5           There was a discussion of the need to  
6 strengthen the education component of the REMS, the  
7 thought that 30 minutes may be inadequate to convey  
8 the appropriate knowledge to ensure the safe  
9 prescription of the medication, and that the  
10 knowledge test should be more rigorous to assess  
11 the key points around safe prescribing are  
12 understood by the prescribers as well as the  
13 pharmacists.

14           With respect to part A and whether  
15 additional studies are needed, I think some on the  
16 committee voice the thought that the Optum and the  
17 CMS data were quite compelling. And suggesting  
18 that there is prescribing to non-tolerant patients,  
19 there was thought to be a need to understand this  
20 better. And some members suggested that more  
21 contemporaneous EMR records, where there's access  
22 to written notes in the record and are available,

1       would be useful in understanding the prescribing of  
2       these medications to patients that appear to be  
3       non-tolerant.

4               I think people were generally in favor of  
5       the idea of doing additional studies on outcomes  
6       using claims and other approaches to understand the  
7       risks associated with these medications in opioid  
8       tolerant versus non-tolerant patients with respect  
9       to the endpoints of overdose, as well as other  
10      adverse opioid-related affects. There's also  
11      thought we need to better characterize the clinical  
12      circumstances where non-tolerant patients are being  
13      prescribed these medications.

14             Anything to add to my summary? Dr. Fry?

15             DR. FRY: I did just want to add if we're  
16      looking back at Optum claims or the CMS study,  
17      starting this year, there's been a lot of  
18      restrictions with opioids, and I've had a lot of  
19      cancer patients paying out of pocket. So none of  
20      that is going to get captured on studies like that  
21      now.

22             DR. BATEMAN: Thank you. And just two other

1 points. Someone suggested that perhaps linked PDMP  
2 data might be useful in this regard, and that would  
3 be a way to pick up some of the prescriptions that  
4 are paid for with cash. And then the idea of a  
5 registry, given the risks associated with this  
6 medication, was put forth and endorsed by some  
7 members.

8 DR. JONIAK-GRANT: Elizabeth Joniak-Grant.  
9 And just to add, when we're talking about  
10 appropriate patients, who are the patients that are  
11 getting it for non-cancer reasons? What are their  
12 diagnoses? Because that's the only way we can kind  
13 of start to determine if it seems appropriate or  
14 not.

15 DR. BATEMAN: Thank you.

16 So we'll move on to objective 2, preventing  
17 inappropriate conversion between TIRF medications.  
18 And the question is, discuss whether the following  
19 strategy will inform if this objective is being  
20 met; further study to obtain dosing instructions  
21 for TIRF dispensed to estimate the number of  
22 inappropriate conversions; and then discuss other

1 strategies the TRIG should undertake to inform this  
2 objective.

3 So this is talking about inappropriate  
4 conversions between medications and the additional  
5 studies we might need in this space to understand  
6 that phenomena and prevent inappropriate  
7 conversions.

8 Dr. Nelson?

9 DR. NELSON: I honestly don't think we have  
10 to study this anymore because it just seems like  
11 it's something we should just fix. Even if it  
12 happens once, it's something that should be  
13 readily -- we just create a set of standards or  
14 guidelines about how things should be converted  
15 amongst one another, and it gets implemented. We  
16 know it happens. I don't think we really need to  
17 know how often it happens. And it doesn't seem  
18 like we need to spend a lot more energy trying to  
19 prove it happens or doesn't happen so often.

20 Just like we do with all of the other  
21 opioids, there are ways to convert from one to  
22 another. I mean, it's a guess. I don't think

1       there's ever going to be an adequate study to  
2       really tell us how to do this. But some group,  
3       maybe FDA, should sit down, and maybe the TIRF  
4       group should sit down and come up with a way to do  
5       this, and just put it out there, and we'll study  
6       that. But I don't think we have to spend much more  
7       time figuring out how common this problem is.

8               DR. BATEMAN: Other comments? Dr.  
9       Kulldorff?

10              DR. KULLDORFF: There was information, I  
11       think it was 9 people, providers, prescribers who  
12       lost their license because they've sort of been  
13       fixing -- and I think it was they didn't provide  
14       the forms from the patients or something like that.

15              I think maybe most serious is if you had a  
16       provider who, for example, prescribes one after the  
17       other or does other errors in the prescribing. So  
18       to hold the prescribers accountable, rather than  
19       focusing on whether the paperwork was done  
20       correctly, it might be more worth focusing on  
21       whether the prescriptions were done correctly,  
22       including this aspect.



1 DR. BATEMAN: Dr. Sandbrink?

2 DR. SANDBRINK: Friedhelm Sandbrink,  
3 Washington, DC. I want to agree with Dr. Nelson,  
4 is that currently, the guidance seems to be that  
5 you cannot take one dosage from one drug to the  
6 other, so I think having guidance in there, what is  
7 the minimum expected dose, or whatever, some kind  
8 of guidance actually for these conversions  
9 specifically I think should be put together if the  
10 data is available. It seems to be also that as we  
11 have prescribing, all TIRF medications seem to be  
12 going down, except one that seems to be going up.  
13 I'm just wondering if this is all conversion to  
14 that one drug or is it new starts into this new  
15 drug?

16 Then related to that, obviously the  
17 conversion data would be specifically -- the  
18 recommendations would be specifically needed  
19 towards this one medication, not in any way to  
20 encourage it or whatever, but if that's what  
21 happening, then I think that's where it's very  
22 important that that guidance is put out.

1 DR. BATEMAN: And my understanding, which we  
2 saw data that there is between TIRF conversions,  
3 but nothing that incorporated information on dose  
4 showing that those were inappropriate conversions,  
5 just that the conversions occurred. So that might  
6 be a next step to do the analyses incorporating  
7 information on dose to really understand the scope  
8 of this problem.

9 DR. BROWN: I'd like to make a comment.

10 DR. BATEMAN: Please?

11 DR. BROWN: One of the questions that I want  
12 to ask is related to -- this is a compliance issue,  
13 and I'm wondering to what extent the FDA is  
14 directly involved with TRIG on an ongoing basis in  
15 determining the strength of compliance and how  
16 compliance is taken care of.

17 DR. BATEMAN: Dr. Hertz?

18 DR. MANZO: We don't specifically look at  
19 conversion. This is Claudia Manzo from OSE.  
20 Compliance with conversion is not one of the issues  
21 that we have been holding the sponsors accountable  
22 for. It's more been around, again, compliance by

1       prescribers with completing the forms. And I'm not  
2       sure if we have the ability to get that sort of  
3       information. We don't have it now on whether it's  
4       being appropriately converted.

5               DR. BROWN: The TRIG is looking at  
6       compliance on an ongoing basis. And since you have  
7       this as one of your objectives, you must consider  
8       it to be quite important. And since they have it  
9       but it's not being done, I just wondered wouldn't  
10      it seem reasonable to move to the next step of  
11      incorporating some more FDA oversight in that.

12             DR. MANZO: At this point we're not really  
13      collecting information on specifically what  
14      products patients are receiving. So again, we  
15      don't have patient enrollment and we're not  
16      following that. And if we're to follow something  
17      like that, it would require enrolling patients,  
18      following the type of medication that they've been  
19      prescribed over time, which would add, obviously,  
20      additional burden.

21             DR. BATEMAN: A comment from Dr. Katzman.

22             DR. KATZMAN: Sure. I'm just wondering if

1       it would be helpful if there could be a study to  
2       develop an equianalgesic dosing for TIRF meds that  
3       can be incorporated to larger opiate equianalgesic  
4       dosing guidelines that would actually be helpful  
5       for clinicians all over the country, because I  
6       think this is what is actually the issue at hand  
7       right now, to be honest in my mind, really, is the  
8       fact that when I see an equianalgesic dosing card  
9       for immediate release and long-acting opiates, I  
10      don't see TIRF meds, nor do most clinicians working  
11      in inpatient and outpatient.

12                So if that was incorporated, I don't think  
13      it would necessarily push clinicians to prescribe,  
14      but it would actually -- it could say for cancer  
15      patients. At least it would be a start for some  
16      educational processes. Thank you.

17                DR. BATEMAN: Dr. Hertz?

18                DR. HERTZ: So even better than a card is a  
19      label. We have this information in the package  
20      inserts for all of these Products. In fact, we  
21      have the risk of medication errors with improper  
22      conversion in a boxed warning. We don't have any

1 control over the kind of cards that get circulated  
2 for equianalgesic conversions. And in fact, we  
3 don't really believe in equianalgesic conversions.  
4 Most of our labels describe the kind of conversion  
5 that was used in clinical studies and found to be  
6 safe that are specifically not equianalgesic  
7 conversions, but safe conversions because there's a  
8 variety of factors that get taken into account.

9 With regard to these, though, each one of  
10 these products has information on how to start  
11 them, and where conversion from another product is  
12 appropriate or not, and how to do that. Of course,  
13 I have no idea how to get prescribers to look at  
14 our labels because I think that would solve a lot  
15 of our problems, but the information is available.

16 DR. BATEMAN: Dr. Goudra?

17 DR. GOUDRA: Basavana Goudra from pain  
18 medicine. I'm not sure about the feasibility of  
19 doing a study like this. Considering that it was  
20 6,000 patients who get these medications to start  
21 with, you're looking at a very heterogeneous  
22 population of cancer patients and trying to consent

1       them for doing this interconversion of dosing  
2       studies. I'm not too sure why that it is  
3       worthwhile or whether patients would be even  
4       willing to participate in a study, or we should be  
5       even doing a study like this.

6               If I'm one of those, I don't think I'm  
7       willing to get into a study of interconversion of  
8       the opioid doses. And if you look at the  
9       literature, there is already a big difference in  
10      one drug being 70 percent more efficacious than the  
11      other one. I don't think we should be going in  
12      this direction, trying to figure out any studies  
13      like this in cancer patients, terminal cancer  
14      patients.

15             DR. BATEMAN: Dr. Craig?

16             DR. CRAIG: Dr. Hertz kind of stole my  
17      thunder, but I was just going to mention that there  
18      already is some recommendations. Fentora PR, for  
19      example, I know recommends a conversion between  
20      Actiq and Fentora. I agree with Dr. Nelson.

21             I'm not really sure that this really makes a  
22      lot of sense to continue to be an important element

1 to look at and evaluate because it probably happens  
2 with some infrequency. And to determine what's  
3 inappropriate, you figure out what is appropriate.  
4 And I think that we've struggled with figuring out  
5 what, first, is appropriate. So that's a  
6 limitation.

7 Number two, I don't think that the quote,  
8 "inappropriate conversion" happens at that  
9 frequency. And without any significant evidence  
10 that there is harm with this conversion, although  
11 there probably is, I think it just happens so  
12 infrequent, it's probably not worthwhile to look  
13 at.

14 DR. BATEMAN: So Dr. Hertz mentioned that  
15 the information is available. So what is the  
16 strategy to convey that information to prescribers?

17 DR. SANDBRINK: Friedhelm Sandbrink. The  
18 strategy I assume would have to be to make sure  
19 that to the provider education piece, it gets very  
20 clearly stated where that information is and how to  
21 get it. It seems to be that that's where it needs  
22 to be. That's what we disseminate to providers.

1       We make them pass the test. So I think if we can  
2       get it in there -- and maybe it's in there  
3       already -- then that's how they can access it.

4               DR. BATEMAN: Dr. Nelson?

5               DR. NELSON: I agree with you that these  
6       prescribing information documents are quite  
7       daunting to read, but people are very facile with  
8       apps and websites and things like that. And if  
9       there was an easy way to do this, I don't think it  
10      would be a tall order to create something that  
11      people would be able to go and look at if they  
12      wanted to do it. I think to go back to the  
13      prescribing information for each of these would be  
14      a lot of work, but there's got to be a way to put  
15      something together that's not that much work.

16              DR. HERTZ? This is Sharon Hertz. I just  
17      would like to say Drugs at FDA is available, and  
18      our package inserts have a highlight section that's  
19      pretty brief. Most products, it's a half a page.  
20      For some of our products with more extensive  
21      warnings, it can be a little bit longer. So you  
22      don't have to go through the entire document. The



1 highlights will give you the key elements, and that  
2 includes critical items about dosing.

3 So we're trying to make it easier than the  
4 old days where the dosing and all that information  
5 was sort of at the very end of a long document.  
6 Now you just have to look at the front page, and  
7 maybe somebody can come up with a better app than  
8 having to go to Drugs at FDA, but at least it is  
9 available electronically pretty easily.

10 DR. NELSON: It's Lewis Nelson, by the way.  
11 But if I could just respond, you're right. For  
12 somebody motivated enough to go and do that,  
13 there's no question that it's much more user  
14 friendly than it's ever been. But it's still a lot  
15 more than most people are willing and able to do.  
16 It would be worth maybe looking at it from, say, a  
17 human performance perspective, or whatever it is,  
18 like how people think, because I just am not sure  
19 it's really consistent with the way people's  
20 workflow is, particularly younger physicians,  
21 younger prescribers, millennials. They don't work  
22 the way you and I work. Not that we're old, but

1 we're not millennials. And they just have a very  
2 different way of thinking, and I'm not sure that  
3 that's the way that they would approach it. I  
4 think the app idea, maybe it's something to look at  
5 and how people think.

6 DR. BATEMAN: One more comment on this  
7 section. Dr. Litman?

8 DR. LITMAN: Thanks. Ron Litman. I just  
9 have to express my doubts why any of these things  
10 would be worth -- and would work. I would hope or  
11 imagine that the vast majority of physicians or  
12 nurse practitioners that prescribe these kinds of  
13 drugs and have experience with them have their pain  
14 patient populations, and they know -- like I know  
15 what anesthetic to give and the relative potencies.  
16 I would imagine that they would know. The kinds of  
17 people that we're thinking about here that, oh, I  
18 need to switch. Let me just go look it up. I  
19 don't know. I just can't imagine that that's very  
20 many.

21 Sharon, you're right. We need a whole week  
22 conference to figure out how to get physicians to

1 look at the labels. We don't. We get experience,  
2 and we go from there.

3 DR. BATEMAN: To summarize on objective 2,  
4 we in our discussion talked about the fact that  
5 we've seen data to suggest that conversion occurs,  
6 although the extent to which this is inappropriate  
7 will require additional analyses that incorporate  
8 data regarding dosing.

9 We heard that there is information available  
10 on the label and other sources regarding safe  
11 conversion between the TIRF products, and some of  
12 the challenges in getting people to access that  
13 information was brought forward. The suggestion  
14 was made that as part of the provider application  
15 education, there should be more robust education  
16 about conversion and about how to obtain  
17 information regarding how to perform conversion in  
18 a safe fashion. And then the suggestion was made  
19 that we need to explore other more accessible ways  
20 of making this information available like the use  
21 of the apps.

22 Anything else to add to that summary?

1 (No response.)

2 DR. BATEMAN: Okay. We're close to 3:30, so  
3 we're at a good time point for a break. So we'll  
4 take a 15-minute break, returning at 3:40. As a  
5 reminder to the panel members, please remember that  
6 there should be no discussion of the meeting topic  
7 during the break amongst yourselves or with any  
8 members of the audience. We'll resume at 3:40.

9 (Whereupon, at 3:39 p.m., a recess was  
10 taken.)

11 DR. BATEMAN: We'll get started again.  
12 We'll now turn to objective 3, preventing  
13 accidental exposure to children and others for whom  
14 it was not prescribed. Part E, discuss whether the  
15 addition of multiple approaches to identify these  
16 rare events will inform if this objective is being  
17 met, and then discuss other strategies the TRIG  
18 should undertake to inform this objective.

19 Dr. Meisel?

20 DR. MEISEL: Steve Meisel. This is one of  
21 the areas where I'm actually reasonably impressed  
22 that the data are as good as they are. We're never

1       going to get perfect on accidental exposures to  
2       kids. Until we get to some star-trekkie [ph] DNA,  
3       bio-ID drug release, no matter what we do about  
4       packaging and instructions or whatever, there's  
5       going to be somebody who leaves it in the wrong  
6       place, and the kid gets a hold of it, and then that  
7       sort of thing.

8               The numbers that we've seen are really quite  
9       small compared to what it could be. I'm actually  
10      more concerned about the intended use in kids.  
11      There were more intended uses in kids that were  
12      beyond the package insert, and many of us would say  
13      inappropriate, then there were accidental exposures  
14      to kids. Again, that goes back to what we talked  
15      about under question 1. And if we can find a way  
16      of prior authorization or tightening up the  
17      utilization at the forefront, to me, will then  
18      reduce the exposure that we're seeing in kids from  
19      controllable ways.

20             I think the accidental stuff that happens at  
21      home, it's low. Could it get lower? Probably, but  
22      we're never going to get to zero on that.

1 DR. BATEMAN: Other comments? Dr. Fry?

2 DR. FRY: Michael Fry, Providence Health and  
3 Services. I just think the most important point  
4 here, as it is with any opioids nowadays, it's  
5 education, educating patients on disposal,  
6 take-back boxes, and the use of naloxone for those  
7 other situations.

8 DR. BATEMAN: Dr. Arfken?

9 DR. ARFKEN: Cynthia Arfken, Wayne State  
10 University. I just want to support the FDA in  
11 their suggestions of other data sources to monitor  
12 this both for the non-fatal and the fatal  
13 overdoses; that it would be among children as well  
14 as among adults and also looking at the death  
15 certificates.

16 DR. BATEMAN: So what other data sources do  
17 you have in mind? Death certificate data?

18 DR. ARFKEN: They had mentioned some in  
19 their future studies, and those sound quite  
20 appropriate to me.

21 DR. BATEMAN: Dr. Nelson?

22 DR. NELSON: Thanks. Lewis Nelson from

1 Rutgers. I think that the data we have, again, is  
2 pretty good and representative. We know that this  
3 is an uncommon occurrence. We know it could be  
4 very problematic. Certainly looking at multiple  
5 data sources helps. If we can get into the EHR, if  
6 we could somehow get better access to those sorts  
7 of datasets. But the poison center's data is  
8 pretty good, and we know how to extrapolate that  
9 out.

10 Like a lot of easy to manage overdoses,  
11 poisonings, we might not get a lot of calls on  
12 these things because doctors know how to manage it.  
13 Parents or family members often call us for these  
14 sorts of things. So we do have a good sense, at  
15 least, from the community about how common these  
16 are. So I feel okay about the data that we have.

17 In terms of preventing -- and I can tell you  
18 one thing from the poison center world, to address  
19 what Steve said, the only way to prevent childhood  
20 poisonings is to get rid of children, honestly,  
21 because kids are just so inventive and so able to  
22 do these things, and we're not creative enough to

1 stop it from happening. And we put out a lot of  
2 poison prevention information. We like lockboxes  
3 and all of these other things. And short of this  
4 star trek time release thing, we're really very  
5 limited in our ability to prevent anything.

6 We do have to educate, and I love the idea  
7 of having potentially naloxone available if there's  
8 a kid at home. It would be a fine thing to do.  
9 But I think the idea that we're ever going to  
10 prevent this from happening is probably a pipe  
11 dream. In terms of preventing others from using  
12 it, that is completely unpreventable, obviously.  
13 If somebody wants to give it away, or sell it, or  
14 steal it, we'll never be able to prevent that.

15 Again, the data sets, I think what we have  
16 to inform this are pretty good. I'm not sure we  
17 need a lot better data to say that these happen;  
18 they're rare. Presumably, maybe not the diversion,  
19 but certainly the pediatric exposures are rare.  
20 And I think we should work hard towards the things  
21 we've already talked about to try to prevent them  
22 from occurring.



1 DR. BATEMAN: Dr. Joniak-Grant?

2 DR. JONIAK-GRANT: Elizabeth Joniak-Grant.

3 I think one thing that would help is just easier  
4 ways to dispose of unused medications. A lot of  
5 times there's these programs, and places say that  
6 they accept them. And you go there, and whoever's  
7 working the front line looks at you and says, "What  
8 are you talking about? I have no idea what you're  
9 talking about." Or you go to a place and they say,  
10 "Oh, well we don't do that. Just the store across  
11 town does that."

12 So I know a lot of people where it's really  
13 difficult to find a place that will actually take  
14 the medication, so a lot of people end up just  
15 taking them back home and put it in the back of a  
16 closet and go, "Well, I'll try again next month,"  
17 or in two months. So if we could kind of  
18 streamline that process, that would be useful, too.

19 DR. BATEMAN: Dr. Brown?

20 DR. BROWN: I would predict that if there  
21 are more prescriptions, there will be more  
22 poisonings. So if there's an increase in the

1       number of prescriptions, if we get excited about  
2       treating breakthrough cancer pain, there will be  
3       more poisonings in children because children are  
4       extremely bright. They're much brighter than we  
5       are.

6               I would suggest that if there is a child in  
7       the house, that we co-prescribe naloxone with these  
8       for the purpose that naloxone is cheap, and you  
9       could save a life if there's going to be a kid in  
10      the house, because they will find an opioid.

11             DR. BATEMAN: Dr. Katzman?

12             DR. KATZMAN: Thank you. My sense is that  
13      there's a good majority of these people that are  
14      misusing this medication as well, and are not  
15      taking it for its intended use, and that are giving  
16      it to a family member or friend for free. And I  
17      would strongly recommend naloxone not only for  
18      children but also for friends or relatives.

19             I don't know if there's any way to add the  
20      education to the prescriber or to the patient.  
21      That would be something to be considered. And in  
22      the CDC guidelines, the doses are surely higher

1       than 50 or 90 morphine milligram equivalents, and  
2       we know naloxone works for everybody. So I echo  
3       everyone's comments on the naloxone. Thank you.

4               DR. BATEMAN: Dr. Sandbrink?

5               DR. SANDBRINK: Friedhelm Sandbrink, DC.  
6       This morning, I was struck by the slide CC-94,  
7       which basically said about the non-medical use by  
8       college students, third quarter 2017, that the  
9       prevalence of having used a TIRF medication is  
10      2 percent in our college students. I find that  
11      extremely high given that only 5,000 people in this  
12      country get this medication. And correct me,  
13      please, if that's the issue here, but it's  
14      certainly less than the other ones, but not that  
15      much less. It really is in the same way.

16              What I'm getting at is that somehow, despite  
17      this rather rare instance where this is being  
18      prescribed, it still makes it in toward a  
19      population that should not have any access to these  
20      kind of drugs. We're not talking about college  
21      students with cancer, presumably.

22              So anyway, maybe I misinterpret the data,

1 but I fear that maybe one way -- if you're talking  
2 about providers having to certify that they're not  
3 going to prescribe it in the patient, or that a  
4 certain patient is actually opioid tolerant, maybe  
5 patients will have to certify that they truly have  
6 a lockbox at home, not just being informed about  
7 this, but that they truly will make sure it's not  
8 going to be lying in there medicine cabinet.

9 DR. KULLDORFF: That number must be wrong  
10 because there are 20 million college students or  
11 2 percent is 400,000 students. And that's just  
12 unrealistic that there will be that many students  
13 taking TIRF. So something is wrong with that  
14 number.

15 DR. BATEMAN: Is that 2 percent prevalence  
16 amongst those that are misusing opioids that are  
17 college students or that's the general --

18 DR. SANBRINK: Can we pull up the slide?  
19 Are we allowed to do that, CC-94?

20 MR. SHERMAN: Dr. Dart?

21 DR. DART: Yes. So that is among people who  
22 endorsed non-medical use; 2 percent were the TIRF

1 products. I still think that there's some  
2 misclassification bias here because I'm not sure  
3 that students can differentiate fentanyl from  
4 transmucosal fentanyl.

5 DR. BATEMAN: So that's 2 percent amongst  
6 those that are misusing opioids.

7 DR. DART: That's right.

8 (Crosstalk.)

9 DR. DART: People who are misusing opioid,  
10 then 2 percent of them.

11 DR. BATEMAN: Okay. That makes more sense.

12 Any other comments on this objective 3?  
13 Dr. Higgins?

14 DR. HIGGINS: One thing that has been coming  
15 to mind, and I don't know pharmacologically whether  
16 this is even possible, but it seems like we would  
17 really want some sort of way via serum testing to  
18 differentiate between licit and illicit fentanyl.  
19 And I don't know if that's even pharmacologically  
20 possible, but I just wonder if that's something  
21 that the TRIG might also take up.

22 DR. BATEMAN: Any additional comments on

1 objective 3?

2 (No response.)

3 DR. BATEMAN: To summarize, I think there  
4 was enthusiasm expressed by members of the  
5 committee for using additional data sources to  
6 better define the frequency of the poisonings  
7 amongst children, using death certificates,  
8 emergency department claims, and EMR records.  
9 People voiced the feeling that the data that we do  
10 have is somewhat reassuring that these events are  
11 very rare.

12 That said, there was concern about the  
13 frequency of misuse of TIRFs amongst college  
14 students, 2 percent amongst those misusing opioids.  
15 In terms of what the TRIG can do to address this  
16 objective going forward, there was a suggestion  
17 that the educational materials for providers and  
18 prescribers and pharmacists could better encourage  
19 disposal of leftover medications to assure that  
20 they're not accessible and potentially to recommend  
21 co-prescribing naloxone when there are children in  
22 the home for people to dispense the medications.

1 Any other comments to add to that?

2 (No response.)

3 DR. BATEMAN: Okay. So we'll  
4 move -- Dr. Hertz, did you have something?

5 DR. HERTZ: Sharon Hertz. So there are  
6 people listening in all over the place because it's  
7 being broadcast. And apparently there is an app,  
8 Drugs at FDA Express.

9 (Laughter.)

10 DR. HERTZ: So I just wanted to point that  
11 out.

12 DR. BATEMAN: Thank you. So we're going to  
13 move on to objective 4, educating prescribers,  
14 pharmacists, and patients on the potential for  
15 misuse, abuse, addiction, and overdose of the TIRF  
16 medications. Discuss whether the prescriber,  
17 patient, and pharmacy survey results, as well as  
18 the requirements for recertification of prescribers  
19 and pharmacists are sufficient to inform this  
20 objective. Discuss other strategies that the TRIG  
21 should undertake to inform the objective.

22 Dr. Warholak?

1 DR. WARHOLAK: For the question of should we  
2 trust the survey results, my short answer would be  
3 no, just because there's very low response rates.  
4 There's significant non-response bias probably.  
5 And one of the things that I find, as somebody who  
6 does survey research quite often, is that  
7 oftentimes the surveys are not included in our  
8 packets, and I don't remember this one being there.  
9 So I don't know anything about the reliability and  
10 the validity estimates, or the psychometric  
11 analysis to assure that we're actually -- that the  
12 results could be trusted even if we did have a good  
13 response rate.

14 DR. BATEMAN: Dr. Fry?

15 DR. FRY: Michael Fry, Providence Health and  
16 Services. With the follow-up survey with the  
17 pharmacist, it's part of the REMS that a designated  
18 pharmacist signs up the pharmacy. So are these  
19 surveys being presented to that pharmacist, or are  
20 they calling and getting whatever pharmacist  
21 answers the phone who may not have done this  
22 training? There could be -- obviously, most



1        pharmacies have at least two pharmacists, and some  
2        have a lot more than that.

3                DR. STEMHAGEN:    So the invitation goes to  
4        the authorized pharmacist, but we don't want just  
5        that person because their responsibility is to  
6        train their staff.    So they're asked to provide the  
7        invitation to other pharmacists in there group that  
8        do dispense the product.    Those are the  
9        instructions.

10               DR. BATEMAN:    Dr. Craig?

11               DR. CRAIG:    Thank you.    I see this kind of  
12        as a little bit different issue.    I see it kind of  
13        as actually the opposite.    I think what pharmacists  
14        already know about -- and providers know about  
15        fentanyl and patients I think is enough.    I think  
16        it's actually too much about the risks.

17               If I say fentanyl to a cancer patient that  
18        I'm talking to, I have to take 10 steps back before  
19        they swing something at me.    I think because of the  
20        fears about fentanyl, I think that we need to do  
21        maybe the opposite.    I think the risks about  
22        fentanyl, these particular products I think are

1       important, but I think that we should probably take  
2       it a little bit further to say we need to educate  
3       people about why they're appropriate and who  
4       they're appropriate for, not just risks.

5               The discussion number, the one following  
6       this one is about why the trend has gone down.  
7       Fear of opioids is a real problem, and it's real  
8       problem for cancer patients. I talk to the cancer  
9       patients about this every single day. I was doing  
10      that yesterday before I came to this meeting,  
11      telling a patient about why fentanyl patch was safe  
12      for her when she was definitely afraid to take it.

13             So I think that this is an important  
14      element, and I think the survey results are  
15      adequate. But I think if we want people to take  
16      these medications, we need to focus on the risks,  
17      of course, but we need to also make it apparent  
18      about why they're important, to make people  
19      advocates for pharmacists, not to be afraid, and to  
20      make them to be actually a patient advocate to say,  
21      yes, there's risks. However, the second part of  
22      the story is this is important for your cancer

1 pain.

2 DR. BATEMAN: Dr. Brown?

3 DR. BROWN: If we're talking about the  
4 education and the efficacy of the REMS, I think  
5 Lewis said it well -- or I can't remember. I think  
6 it was Lewis. Despite clear labeling, patients  
7 that are not tolerant, patients that are less than  
8 18, and patients that do not have cancer are having  
9 TIRF prescribed. The CMS data shows 72 percent of  
10 the prescriptions were not for cancer.

11 The importance here is the outcome. The  
12 outcome is whether or not the education can be  
13 converted into behavior, which is operative in the  
14 care of a patient. Buprenorphine, 8 hours; TIRF,  
15 30 minutes or something, if we're dealing with an  
16 issue of education and we're truly concerned, that  
17 the FDA is truly concerned about the issue of  
18 safety, then it sounds to me there needs to be more  
19 education, in terms of time, exposure.

20 DR. BATEMAN: Dr. Nelson?

21 DR. NELSON: Thanks. Lewis Nelson from  
22 Rutgers. Thanks, Rae. I think that it is

1       important to provide education. I wonder,  
2       though -- I don't remember the exact numbers, but  
3       there was something like 29,000 pharmacists or  
4       pharmacies around the country that dispensed. It  
5       was some huge number, and I don't really know if  
6       it's practical to think that every one of them is  
7       going to maintain a high level of education.

8               You're right. The initial training for 30  
9       minutes seems a little bit short, but then there's  
10      got to be this ongoing survey reassessment and  
11      education. But I just don't know that for  
12      something that's very low volume for most people,  
13      if they're ever going to be able to maintain that  
14      level of training.

15             We know in heart surgery, places that do a  
16      lot of heart surgery, have better outcomes than  
17      places that do one a month or something. And it's  
18      probably not that much different than anything  
19      else, for example, dispensing a TIRF. And it does  
20      make you wonder whether either we need to have a  
21      just-in-time education program every time  
22      somebody's going to dispense one of these things,

1 particularly if it's been more than a week or a  
2 month or something like that. They have to go  
3 through some sort of checklist in order to make  
4 sure they're doing the right thing.

5 Or maybe we need to change the way we  
6 dispense these things and don't let them be  
7 dispensed from 29,000 pharmacies across the  
8 country, but we do what we do with, say, Xyrem or  
9 some of these other programs, where we have a  
10 controlled dispensing program, where you have  
11 to -- it's a little more complicated. I know there  
12 are access issues, but it works for other  
13 medications that have small numbers of patients  
14 associated with them. And maybe there's a  
15 different approach we should be taking to make sure  
16 that only the right people are getting it.

17 I'm not arguing that prescribers shouldn't  
18 be held more accountable, but often pharmacists  
19 become the filter for poor prescribing habits among  
20 physicians. And this might be one way to control  
21 that a little bit so that we could maintain a high  
22 level of appropriateness in terms of who gets these

1 medications, ultimately.

2 DR. BATEMAN: Dr. Joniak-Grant?

3 DR. JONIAK-GRANT: Elizabeth Joniak-Grant.

4 In addition to having more education for the  
5 doctors. I think we have to remember that when  
6 we're talking about educating the patient, we  
7 really are talking about teaching the patient. I'm  
8 not really sure who goes over the info with the  
9 patient. It's very different to have a doctor go  
10 over it, versus the nurse practitioner, versus  
11 maybe a tech who doesn't know really what the  
12 medication is, or what it's about, or how to spell  
13 it.

14 So to be very clear with whose role this is  
15 and who's considered sufficient, one way to really  
16 be effective with this is to maybe go through it  
17 with the significant things line by line, and stop  
18 and have the patient repeat it back or have the  
19 patient initialize, because a lot of times,  
20 patients just get this wall of information, and  
21 kind of listen, and get lost in it. And if they're  
22 coming in where they actually need a fentanyl

1       prescription, they're probably feeling terrible.  
2       So it's even harder to pay attention, and it's even  
3       harder to really compute.

4               So maybe it would be worthwhile to go over  
5       the top three things next time you see them in case  
6       they don't really remember what was going on. When  
7       you're in severe pain, a lot of that stuff becomes  
8       like, "Yeah, yeah, okay, okay, what do I need to  
9       do?" So I think we have to be really mindful of  
10      that and maybe sort of approach it like we would  
11      like an informed consent, where we touch base and  
12      make sure that they're following, and make sure  
13      that they know what we're talking about.

14             Maybe too, for the pharmacy aspect, just  
15      have the pharmacist go over the opioid tolerance  
16      requirement. There are medications where you have  
17      the mandatory counseling. And it can take 15  
18      seconds. It can take 20 seconds. It doesn't have  
19      to be a long, drawn-out thing, but to just have  
20      that moment to stop and say this is something you  
21      really need to know, I think could be something  
22      that could be worthwhile.

1 DR. BATEMAN: Dr. Brand?

2 DR. BRAND: Paul Brand, Florence, Montana.

3 I'm going to echo some of these where it's asking  
4 whether or not they're sufficient to inform the  
5 objective. Obviously, they're not. I don't think  
6 the issue is in the information that's being given.  
7 I'll repeat that I think the information just needs  
8 to be repeated. Repetition is going to drill that  
9 into the pharmacy, into the prescriber, into the  
10 patient. And we have to remember that the  
11 patients, the qualifying patients, are already on a  
12 narcotic medication, which could affect their  
13 memory, et cetera.

14 So repetition of the information -- the  
15 information looks great, and obviously people are  
16 getting 100 percent on the test when they're  
17 testing, whether it's the prescriber or the  
18 pharmacist, but they're not doing so well on the  
19 follow-up. So every 2 years seems like a long time  
20 for recertification. I think repetition for all of  
21 us would be really good to meet that objective.

22 The other thing, for H, discuss other



1 strategies, it would be good if the TRIG could  
2 discuss, maybe including what to do with unused  
3 medications at the end of a prescription.

4 DR. BATEMAN: Dr. Katzman?

5 DR. KATZMAN: Thank you. Joanna Katzman  
6 from Albuquerque, New Mexico. I think we've spoken  
7 a lot today about how the prescriber and the  
8 pharmacist could educate the patient more about the  
9 risks of these medications, but I think the bigger  
10 question is how do we get the medication more to  
11 the patients who need it, more for the patients  
12 with cancer. And it does seem like there might  
13 be -- but we don't know. There might be geographic  
14 gaps in the country. There might be a  
15 socioeconomic gaps. There might be gaps in age  
16 groups and insurance gaps.

17 It also seems as though there might be gaps  
18 in different medical centers with prescribers, and  
19 it seems like that really is the biggest issue  
20 where patients are being possibly undertreated for  
21 their cancer pain, especially when you see what  
22 Western Europe is doing in terms of their dosing

1       for immediate-release fentanyl.

2               So that's where I think that's one of the  
3       things that would be nice to be able to evaluate.  
4       Programs like Project Echo that I'm very familiar  
5       with have many echoes related to cancer.  
6       MD Anderson and other programs in cancer around the  
7       country have echoes that can educate clinicians  
8       about this kind of thing. And I think education  
9       around this could teach providers about this.  
10      Thank you.

11             DR. BATEMAN: Thank you. Any other comments  
12      on objective 4? Dr. Meisel?

13             DR. MEISEL: Steve Meisel. One other  
14      comment here. I think, Lewis, you mentioned it  
15      earlier that education is critical, but education  
16      doesn't by itself create behavior change. If there  
17      were some systems in place that would force the  
18      concepts into practice in real time, that would be  
19      important.

20             So if you're going to refill a prescription  
21      for one of these things, then you've got to ask  
22      certain kinds of questions as part of not a

1 registry necessarily, but some sort of a prior  
2 authorization program, that sort of thing, that  
3 brings the concepts into being, into real life, and  
4 to make them alive. I think that would then help  
5 to embed those concepts into a working practice;  
6 otherwise, it becomes, "Yeah, I've got to take that  
7 test, and I'm done."

8 I think the fact that there's such a dropoff  
9 from 100 percent, for some of the questions, down  
10 to into 40's. I know there may be some problems  
11 with the survey design or the sample pool of folks  
12 who have been asked the questions, but that's  
13 enormous, in my view, attrition of knowledge. And  
14 the reason there's attrition of knowledge is that  
15 nobody's putting it to use. So how do we put it to  
16 use?

17 DR. BATEMAN: To summarize on point 4, there  
18 was concern by some of the panelists on the  
19 committee about the attrition of knowledge that  
20 occurs over time and a feeling that more rigorous  
21 education may be merited, that 30 minutes every  
22 2 years is not going to be adequate for people to

1 retain the knowledge and use the medications in a  
2 safe way.

3 So there's a suggestion that just-in-time  
4 education might be introduced through the use of  
5 checklists or other mechanisms. There might be  
6 systems-based approaches to ensure that people  
7 recall the components of their education as they  
8 are dispensing the medications. One panelist  
9 suggested that a narrower number of pharmacies  
10 might be authorized to dispense the medication that  
11 have a real expertise in the use of this  
12 medication.

13 There was also discussion about the need to  
14 include in education, the ways in which the  
15 medication might be used appropriately to educate  
16 clinicians about the effectiveness of the  
17 medication for the treatment of cancer pain to  
18 improve access for patients that are likely to  
19 benefit from the medication.

20 Then there was discussion of the need to be  
21 attentive to how the information is conveyed to the  
22 patients, including some assessment of

1       comprehension of the material that's being  
2       conveyed. And then in terms of evaluation, there  
3       was a concern about the response rates and a  
4       feeling that going forward, there should be  
5       approaches to encourage better response rates to  
6       the surveys of providers.

7               Anything else to add to my summary?

8               (No response.)

9               DR. BATEMAN: Okay. So we'll move on to  
10       discussion question 2. The goal of the TIRF REMS  
11       is to mitigate the risk of misuse, abuse,  
12       addiction, overdose, and serious complications due  
13       to medication errors. Considering the substantial  
14       limitations of the surveillance data, discuss the  
15       significance of findings suggestive of increasing  
16       rates of adverse events despite decreasing use of  
17       the TIRF's medications.

18              Dr. Kulldorff?

19              DR. KULLDORFF: So they obviously mean a  
20       different possible explanation for this. But one  
21       possible explanation is if the number of patients  
22       go down, it's the patients with more severe cancer

1       and more severe other things that are the ones that  
2       are remaining on it. They might have a higher  
3       proportion of death, for example. So that's one  
4       possible explanation, that the average patient  
5       population is changing to the more severe as use  
6       decreases. But that's only one possible  
7       explanation. There are other possible explanations  
8       as well.

9               DR. BATEMAN: Dr. Meisel?

10              DR. MEISEL: Steve Meisel. I mentioned this  
11       earlier. I think one of the possibilities, and we  
12       can't answer the question today because we don't  
13       have the data, is are the number of events rising  
14       because of some defect in the REMS program? Is it  
15       rising because of some change in the population  
16       that is unstated or unknown and hasn't been fully  
17       analyzed? Or is it because we now have a different  
18       mix of TIRF products that's being used?

19              This could all be artifacts on the basis of  
20       the fact that now we've got Subsys, and Subsys has  
21       a higher rate of, I don't know, adverse event. We  
22       don't know that. There's no data one way or

1 another on that, but it's certainly a possibility.  
2 It's possible that what Martin talked about before,  
3 about now that we have a different patient  
4 population, that it's making it look like it's  
5 higher than what it is. It could be all sorts of  
6 factors here.

7 So I think trying to ascribe causality or  
8 association with the REMS for the changes in what  
9 we're seeing with death, I think is a risky  
10 proposition that we could really go down a rabbit  
11 hole with really the wrong kinds of conclusions.

12 DR. BATEMAN: Other comments? Dr. Warner?

13 DR. WARNER: I just wanted to comment -- I  
14 made the comment before that I think the data is  
15 acknowledged here to be rather limited. And I  
16 think that somehow there should be better ways to  
17 get this kind of information. I know that I've  
18 been on several of these panels before where ideas  
19 have been generated. So I just wanted to echo that  
20 it's difficult to interpret increasing rates when  
21 the data are limited as they are.

22 DR. BATEMAN: Does anyone want to comment on

1 the stability of the estimates? I think that's one  
2 thing that was impressive to me, that the numbers  
3 that are driving these event rates are extremely  
4 small. Dr. Arfken?

5 DR. ARFKEN: Cynthia Arfken, Wayne State  
6 University. I would just add to it, it's also  
7 difficult in the context that there's a lot of  
8 publicity about fentanyl in general.

9 DR. BATEMAN: Thank you. Any other comments  
10 on the discussion point?

11 (No response.)

12 DR. BATEMAN: Just to summarize, I think  
13 there were a number of plausible explanations put  
14 forth for the findings suggesting increasing rates  
15 of adverse events, including potential changes in  
16 the patient profiles would shift to more high-risk  
17 patients; a heightened awareness of fentanyl and  
18 the adverse effects of fentanyl that might lead to  
19 surveillance bias; changes in the specific TIRFs  
20 that are being used that may have different risk  
21 profiles.

22 Then my own point, just that the data are



1       incredibly sparse, and the estimates of risk are  
2       quite unstable, leading to challenges coming to any  
3       conclusion. One of the panelists made the  
4       recommendation to explore other data sources to  
5       assess whether this increase in risk is in fact  
6       real.

7               Anything else to add on this point?

8               (No response)

9               DR. BATEMAN: Okay. Then we'll move to a  
10       discussion question 3. The REMS assessment data  
11       indicate that outpatient use of TIRF medications  
12       decreased approximately 75 percent since 2010.  
13       Part A, discuss any factors that may have resulted  
14       in the decrease in use of TIRFs medication.  
15       Discuss whether TIRFs REMS may be creating  
16       unnecessary barriers to access to these products  
17       for patients who could benefit from them. And if  
18       so, what can be done to reduce those barriers?  
19       Then part C, discuss whether there are any  
20       additional mechanisms to reduce the burden to the  
21       healthcare system associated with the TIRF REMS.

22               Dr. Nelson?

1 DR. NELSON: Thanks. Lewis Nelson from  
2 Rutgers. Obviously, the numbers are falling, but  
3 as Martin suggested before, there are many  
4 different explanations of why that's occurring.  
5 It's very possible we've just decided these drugs  
6 don't work very well and they're not worth using.  
7 It's also possible that we decided they're too  
8 dangerous, and we have to limit the patient  
9 population that's getting them or we think there  
10 are too many people that are misusing them, or  
11 diverting them, or abusing them.

12 So there are a lot of reasons this could  
13 have occurred. I don't think we have the data to  
14 show us specifically why this is occurring. It's  
15 probably a mix of multiple things just like was  
16 suggested before.

17 The question that is phrased is "unnecessary  
18 barriers." There are barriers. I question whether  
19 they are unnecessary. Like Rae and others have  
20 commented, this is a risk-benefit analysis. There  
21 are potentially benefits. I think we might have to  
22 agree on that. We have to decide, though, in which

1 population the risk is worth taking, and that is a  
2 barrier. And I don't really know any way around  
3 that because if we lowered it so that anybody can  
4 get this at any time, you could imagine it would  
5 just be pure chaos out there, and it would be very  
6 dangerous.

7 So yes, there are barriers. I'm not sure  
8 that they're unnecessary. You've got to find the  
9 right doc. You've got to find the right pharmacy.  
10 You've got to sign the forms. But it could be a  
11 lot worse. And I think given the risks associated  
12 with it, that it's a reasonable place to be.

13 Are there additional mechanisms? I'm really  
14 not convinced that we have enough mechanism in  
15 place currently. I know people -- FDA thinks, yes,  
16 that the REMS is working, and I guess it depends on  
17 your definition of working. I still think that  
18 it's yet to be proven that it's working, and I'm  
19 not convinced we don't have to actually raise the  
20 barrier a little bit.

21 DR. BATEMAN: Dr. Higgins?

22 DR. HIGGINS: I completely agree. I think

1       there's just not enough data to know exactly what  
2       are the reasons for this. One possibility could be  
3       that there's less of a perceived need. There are  
4       many more alternative therapies. There's  
5       intranasal ketamine, which is not readily available  
6       yet, but it's coming along the way. So that's a  
7       possibility.

8               With respect to the burden on providers, I  
9       think we've come up with a number of suggestions  
10      today about how to make the education and  
11      recertification process more organic, integrative,  
12      and a bit easier, and also happening more  
13      frequently, which would instill the knowledge and  
14      retain the knowledge in an easier fashion.

15             So I would take to heart all of the  
16      suggestions that we've had today about making it  
17      more integrative and organic with respect to  
18      education, the recertification process.

19             DR. BATEMAN: Dr. Warholak?

20             DR. WARHOLAK: So one of the things I was  
21      thinking about is that definitely there could be  
22      many, many reasons for this, not the least of which

1 is all the press that fentanyl has gotten. Then  
2 there's also some other systems in place that may  
3 or may not be helping with this.

4 For example, pharmacy benefit managers in  
5 the prior authorization process, there are pharmacy  
6 benefit managers for certain plans. Unless there's  
7 a cancer diagnosis, then basically the claim stops  
8 processing. And I don't know if eventually you can  
9 get through that or not. I'm not convinced that's  
10 actually a bad thing. And they also look to make  
11 sure that the patient is not opioid naive as well.  
12 So there are a lot of other things that could be  
13 going on here.

14 DR. BATEMAN: Dr. Joniak-Grant?

15 DR. JONIAK-GRANT: Elizabeth Joniak-Grant.  
16 I know a reasonable amount of patients who have  
17 gone in to have prescription filled for opioids,  
18 where individual pharmacists have denied them.  
19 They've refused to fill them, and they have kept  
20 the prescriptions. So I'm wondering if this is  
21 happening in any cases with TIRF, and I'm guessing  
22 that people on the panel would have a better grasp

1 on this if you've heard this from patients or if  
2 you're aware of any data where this is going on,  
3 where the pharmacist just refuses to fill the  
4 prescription, and not because it won't go through  
5 insurance.

6 DR. BATEMAN: Dr. Meisel?

7 DR. MEISEL: Steve Meisel. In terms of the  
8 barriers, I guess I don't really see the -- I'm  
9 with Dr. Nelson on this. I'm not sure that this is  
10 really that much of a barrier. In my state, we  
11 have medical cannabis, and docs have to become  
12 certified folks to authorize medical cannabis, and  
13 that's work. And getting people into the medical  
14 cannabis program is work, but it happens. We have  
15 it with thousands of patients, and they do it.

16 For a hospice, to recertify a patient for  
17 hospice is a mountain of paperwork on the part of  
18 the hospice staff and docs, but they do it.  
19 Compared to that, this is relatively nothing. So  
20 if it's thought to be of value, it will happen.  
21 This isn't that big of a barrier.

22 I think some of the reasons that the

1 utilization has gone down, go back to the basics.  
2 This is a very expensive product. You're talking  
3 about something that's \$100 a dose or something for  
4 some of these. A lot of the population might be in  
5 the hospice setting where the payment is capitated.  
6 You get so many dollars per day, and the drugs come  
7 out of that. So the hospice is not going to pay  
8 for this when they can pay for roxanol or  
9 something. And could argue about the relative  
10 efficacy of this versus roxanol, but that's a whole  
11 lot cheaper when you're allocating your hospice  
12 dollars.

13 Folks just don't find the clinical value  
14 compared to other drugs. If they did, these  
15 barriers are minor. So the reasons the utilization  
16 isn't where it is lower and it's lower than it used  
17 to be, in part, it's the fentanyl stigma. In part,  
18 I think pointing the finger at the REMS and all  
19 that as barriers. I think it's a red herring. I  
20 think it's perception of relative clinical value  
21 and cost.

22 DR. BATEMAN: Dr. Brown?

1 DR. BROWN: I think if there are barriers to  
2 this drug or this class of drugs, they're not  
3 unnecessary barriers. They're reasonable barriers,  
4 and they're reasonable barriers based on our  
5 assessment of, as I said before, benefit versus  
6 risk.

7 One thing that I don't want the agency to  
8 focus on is trying imply that there's unnecessary  
9 barriers to this drug without scientific evidence  
10 because we haven't heard any scientific evidence  
11 that there is a barrier to folks getting this drug.

12 What we occasionally hear, and I think what  
13 the agency probably has heard, is individuals  
14 coming to the agency or in professional  
15 organizations saying we got a problem with  
16 unnecessary barriers to the dispensation of this  
17 drug. And that's not scientific evidence, and it  
18 occurs to me that we need to make certain that we  
19 do the science first.

20 DR. BATEMAN: Dr. Katzman? Dr. Arfken?

21 DR. ARFKEN: Dr. Arfken, Wayne State  
22 University. I'm concerned about the very steep and



1       stable decline in the number of prescribers, and I  
2       don't know if that has opened up in a geographic or  
3       other way inequalities of access to treatment. I  
4       would also want to know what are the alternatives  
5       that prescribers are using for breakthrough pain in  
6       cancer.

7               DR. BATEMAN: Dr. Habel?

8               DR. HABEL: Laurel Habel, Kaiser Permanente.  
9       I also agree with some of the other statements that  
10      have been made that we really have a lack of  
11      evidence at this point about the barriers. And I  
12      don't know whether or not the surveys that are  
13      currently being done to the prescribers and the  
14      pharmacists and the patients could add questions  
15      about barriers.

16              I know there are questions about safety and  
17      inappropriate prescribing, but I don't know whether  
18      or not there are questions about barriers. And if  
19      not, if that could be added. Of course, there is a  
20      problem with response rates, and I would also hope  
21      that response rates could somehow be increased.  
22      But that's my idea.

1 DR. BATEMAN: Dr. Litman?

2 DR. LITMAN: Thank you. Ron Litman. So A,  
3 I think that it's my sense that opioids have been  
4 decreasing in frequency. And a lot of the data  
5 that's been presented here wasn't as recent as 2016  
6 or '17, like the CMS data. And it wasn't really  
7 until these last couple of years that -- opioids  
8 have been in the public eye for a while now, but  
9 there's really been an intense push to limit them.  
10 The CDC came out with their new guidelines as to  
11 the Joint Commission in 2017, and I think it's  
12 really -- like the insurance company started  
13 limiting them and state societies.

14 My sense is that that's probably the main  
15 reason. Plus also there are the sunshine laws and  
16 doctors not wanting to be associated with  
17 prescribing medicines if they have  
18 relationships -- if they've received either money  
19 or other products of value from drug companies.  
20 And I think that's really scared a lot of  
21 physicians from prescribing these.

22 B, whether or not these have been

1 unnecessary barriers, it's hard to know. Could it  
2 be that some physicians have stopped prescribing  
3 them because of the reasons I just mentioned, but  
4 their patients still need it? I just don't know.  
5 I can't think of a way to tell that.

6 C, additional mechanisms to reduce the  
7 burden, I agree with Dr. Brown. I think we've got  
8 pretty good mechanisms right now. And if you're in  
9 practice and your patients need this, then -- I put  
10 myself in their place, and I'm not a pain physician  
11 or I have a practice like that. But I would  
12 certainly make sure that my patients who had that  
13 kind of breakthrough pain had this available. So  
14 I'm not sure what else we could do to reduce that  
15 burden.

16 DR. BATEMAN: Dr. Goudra?

17 DR. GOUDRA: Dr. Goudra from pain medicine.  
18 There are two issues here I think, and having  
19 worked both in England and here, I mainly work in  
20 the endoscopy area. What I observed is  
21 [indiscernible], and I believe it. When I was in  
22 England, I could ask for fentanyl for every

1 endoscopy case or every minor case, whether I'm  
2 going to use it or not. If I don't use it, I just  
3 give it back, and the tech will take it and  
4 document it.

5 Here, because of the various -- I don't know  
6 whether you call it barriers, or checks and  
7 balances, or whatever it is, I think 10 times  
8 before I'm going to take fentanyl, even if I think  
9 there could be a relative indication for somebody  
10 undergoing endoscopy with maybe and surgery for an  
11 irritable airway. Because I have to think, one, if  
12 I don't use it, I have to waste it, which, believe  
13 it or not, it is a barrier. And many of my  
14 colleagues tend to think similarly.

15 So it depends, whether we look at it as  
16 checks and balances, or barriers, the easiest way  
17 is probably going to the people because the  
18 majority of the decline has been in the  
19 prescribers. It's probably not that difficult to  
20 go and ask questions as to why they're dropping  
21 out.

22 DR. BATEMAN: Dr. Craig?

1 DR. CRAIG: I think barriers are probably  
2 not necessarily related to the REMS. I think  
3 probably it was the tipping point that started the  
4 slide, started the trend. I think barriers, at  
5 least what I see in my institution, is just fear,  
6 fear by patients, fear by providers about I'm going  
7 to be monitored, and I'm going to be tracked, and I  
8 have to do all this stuff that I didn't have to do  
9 before.

10 Some of the people make the point that  
11 people would continue to do that if there was a  
12 reason to do it. In essence, the benefit outweighs  
13 the risks. And in this scenario, there are other  
14 alternatives that people can use that are readily  
15 available, that are less expensive, that are less  
16 quote/unquote "monitored and less risky."

17 So I think that that's also a trend, and I  
18 think that there are issues that are surrounding  
19 the TIRF REMS that probably led to the decline  
20 rather than the program itself.

21 DR. BATEMAN: Dr. Sandbrink?

22 DR. SANDBRINK: Friedhelm Sandbrink,

1 Washington, DC. It seems to be that my observation  
2 is that that the oncologist and the palliative care  
3 community is not really making use of this  
4 medication. There are few indications. Eight  
5 percent of the prescribers, only 8 percent are  
6 oncologists. The largest are anesthesiologists  
7 pain physicians who probably, presumably, primarily  
8 treat chronic non-cancer pain.

9 There's also this observation that we have  
10 about 5[000] to 6,000 prescriptions with about  
11 4[000] to 5,000 prescribers. That's about 1  
12 patient per prescriber. It seems to be that the  
13 oncologists or palliative care groups who see lots  
14 of patients don't seem to make use of it.

15 This is now superimposed. We see the trend  
16 that for non-cancer chronic pain, there is much  
17 less reliance on opioid medication, and I would  
18 assume that the providers who have their patients  
19 in that situation are gradually dropping them off.  
20 The patients that are on it already, dependent on  
21 this and high-dose opioid prescribing, they're  
22 probably maintained for a while, but they're not

1 starting new patients. And as they don't have  
2 patients anymore on this, they fall off.

3 That at least is my suspicion here, but it  
4 comes back to probably relatively low penetration  
5 of use in the oncologist and palliative care  
6 setting out of several reasons that were already  
7 discussed probably.

8 DR. BATEMAN: Any further comments on  
9 question 3?

10 (No response.)

11 DR. BATEMAN: Then I'll go ahead and  
12 summarize. The committee discussed multiple  
13 potential explanations for the decrease in  
14 prescribing of TIRFs medications that's been  
15 observed since 2010. One explanation is more  
16 appropriate use, and I'd note this is something  
17 that can probably be evaluated using longitudinal  
18 claims data sets.

19 We saw a little bit of that in the CMS data,  
20 but using something like Optum or Truven data, you  
21 could look at prescribing in association with  
22 different indications over time and understand

1       whether the shift represents a decrease primarily  
2       in the use for non-cancer pain or whether it's a  
3       scene for cancer pain as well.

4               It could be attributable to changes in  
5       pharmacy benefits or changes in the perception of  
6       the benefits of the medication relative to the  
7       expense of the medications, as well as changes in  
8       the way people think about fentanyl and some of the  
9       stigma attached to fentanyl.

10              The committee talked about barriers  
11       associated with the REMS program, and I think the  
12       general consensus was that although there are  
13       barriers associated with the program, these are  
14       reasonable given the risks associated with the  
15       medication. Although some of the committee voiced  
16       concern about the decrease in the number of  
17       prescribers who are REMS certified and a need to  
18       better evaluate the reason for that decline, as  
19       well as to obtain additional data recording  
20       barriers that the REMS program may create.

21              Anything to add to my summary?

22              (No response.)



1 DR. BATEMAN: So then, we'll move on to  
2 question 4, the final question. The TIRF REMS  
3 requires that prescribers and pharmacists are  
4 educated on the risks and safe use of TIRF  
5 medications prior to prescribing and dispensing and  
6 that patients sign a form acknowledging that  
7 they've been made aware of the risks and methods  
8 for safe use.

9 A, given the limitations of the assessment  
10 data and the limited use of these products, discuss  
11 whether the goals and objectives of the TIRF REMS  
12 are still appropriate;; and B, if you believe the  
13 goals and objectives remain appropriate, discuss  
14 whether you believe the TIRF REMS is adequately  
15 designed, i.e., ensuring prescribers, pharmacists,  
16 and patients are educated to achieve these goals.

17 I think we've touched on a lot of these  
18 points in our earlier discussion, but perhaps we  
19 can just summarize our perspectives on these points  
20 regarding the effectiveness of the REMS program  
21 overall, starting with Dr. Litman.

22 DR. LITMAN: Thank you. Just a quick

1     parting comment about physician education. We have  
2     so much physician education. It seems like every  
3     other day we're getting an email about another of  
4     what we call learning links. It takes up a lot of  
5     our time. I am very skeptical and cynical about  
6     the usefulness of these.

7             Like I kind of alluded to before, I think  
8     that if you're in the business of giving TIRFs to  
9     your patients, chances are pretty good you don't  
10    need to take an 11-question multiple choice. I  
11    would love to see the questions before. You guys  
12    said that you had them, but you didn't show him.  
13    But if they're anything like the questions I have  
14    to go through about hand washing --

15            (Laughter.)

16            DR. LITMAN: -- then it's really just  
17    infection control. It's really endless, and we  
18    take quite a cynical approach to it.

19            As far as the patient form goes, I can't  
20    speak to that, but I would come close to saying  
21    that if you're a patient with such severe pain,  
22    that it's ruining your life and you have to take

1       these drugs, then I'm not going to read every  
2       detail and worry about some of the stipulations on  
3       the contract.

4               So in essence, I think they are worthy  
5       goals, of course, but I don't think that they're  
6       very effective. I don't see any evidence that they  
7       are.

8               DR. BATEMAN: Dr. Brown?

9               DR. BROWN: I agree with Dr. Litman. I'll  
10       have to say that I think the TRIG is doing a  
11       yeoman's work, and I really appreciate the work  
12       they've done in putting this together. I see that,  
13       after going through all of this data, how difficult  
14       it is to make an assessment on surveillance data.  
15       And I'm a little bit concerned that the TRIG may  
16       not have the availability of all the data that's  
17       required to continue to do the good work that  
18       you're currently doing.

19               I want to ensure that we continue to focus  
20       on the fact that education is an important topic  
21       here, and if we can -- I'm concerned that if we  
22       don't improve the education of these people that

1       are prescribing TIRFs, that we will begin to see an  
2       increase in prescriptions and more adverse  
3       outcomes.

4               DR. BATEMAN:   Dr. Joniak-Grant?

5               DR. JONIAK-GRANT:   Elizabeth Joniak-Grant.

6       I think the goals and objectives are good.  It  
7       concerns me that -- I think it was 43 percent of  
8       patients know that they have to stop the TIRF if  
9       they stop around-the-clock opioid use.  We're  
10      taught a lot that patients have to be their own  
11      advocates, and I think there are some important  
12      things that we need to be really sure that patients  
13      do know.

14              I think basically just to point back to what  
15      was said when we discussed the objective 4, I think  
16      that addressed a lot of what we were talking about  
17      here, about how we could do that as sort of  
18      checking in, doing repetition with it, maybe having  
19      the pharmacist go over the key elements would be  
20      worthwhile.  But the other thing is, we keep  
21      talking about this 30-minute training, but I highly  
22      doubt it's 30 minutes.  Whenever you get those

1 video things and they say, oh, it's 30 minutes,  
2 they never take 30 minutes. They take 15, maybe 20  
3 at the most.

4 So I think we should also be mindful that  
5 people scan through. They go, "Oh, this is what it  
6 is. Oh, this is what it is." So it's very  
7 unlikely that it's even 30 minutes.

8 DR. BATEMAN: Dr. Nelson?

9 DR. NELSON: Thanks. I don't have that much  
10 more to add to what's already been said. I do only  
11 think that there are a lot of perverse incentives  
12 on the way we practice medicine. I don't think  
13 that education is the solution. Clearly, we have  
14 to educate, but people do a lot of things they know  
15 they shouldn't do, and I'm not sure that no matter  
16 what we tell them to do or not to do, they're going  
17 to do what they want to do.

18 For the things that they're ignorant about,  
19 we should certainly try to educate them about it.  
20 But as we've learned, these are smart people that  
21 are still getting 40 percent scores on these exams,  
22 and these are folks who are highly trained in their

1 specialties, and they still don't know the basics.  
2 I just don't think it's going to really ever fix  
3 the problem. We need to do more than just educate.

4 Again, as I said earlier, there's just too  
5 many perverse incentives on the things that we do  
6 when it comes to the practice of medicine, and we  
7 have to fix those, not necessarily fix these. And  
8 I don't know how we're going to be able to fix  
9 those things. Maybe that's a little dark as a way  
10 to end the day, but, really, we just have to make  
11 sure that these medications are used safely and  
12 appropriately.

13 DR. BATEMAN: Dr. Gouda?

14 DR. GOUDA: Dr. Gouda, pain medicine. Just  
15 to support what Dr. Litman said, just to  
16 [indiscernible] here, any anesthesiologist who  
17 tries to consent the patients for label of  
18 analgesia [indiscernible] knows very well they're  
19 not really in a mood to listen to what are you're  
20 saying. All they want is to get rid of the pain.  
21 So that's something very similar, trying to get  
22 somebody in acute breakthrough pain. Maybe in

1       between the pain, that's another issue.

2               The second thing is, if I'm going to try any  
3       new drug, for example, [indiscernible], that came a  
4       few years ago, I look myself to get as much  
5       information as it's available before I use it. So  
6       as a result, I don't think it's any point in trying  
7       to re-educate physicians who have spent years and  
8       years in training and try to teach them something  
9       new. They know very well both the patients and the  
10      medication they're going to use.

11             DR. BATEMAN: Dr. Meisel?

12             DR. MEISEL: Steve Meisel. I'm going back  
13      to the -- and we've actually seen this slide  
14      several places -- one of the slides from FDA on the  
15      goals and objectives of the TIRF REMS. The goals  
16      are to mitigate the risk of misuse, abuse,  
17      addiction, overdose, and serious complications by  
18      prescribing and dispensing TIRF meds only to  
19      appropriate patients, preventing inappropriate  
20      conversion, preventing accidental exposure to kids  
21      and others for whom it's not prescribed, and  
22      educating prescribers, pharmacists, and patients on

1 all those things.

2 I think clearly we can educate, but  
3 education is not -- we've talked about that to  
4 death. We may have done some good work about  
5 accidental exposure to kids. I think the data on  
6 that is relatively strong, but we certainly haven't  
7 accomplished the stronger ones, to make sure that  
8 prescribing and dispensing TIRF meds only to  
9 appropriate patients is what we do. And by  
10 corollary, don't dispense it and prescribe it to  
11 those who are inappropriate, and preventing  
12 inappropriate conversions.

13 The only way to do that is to change how we  
14 do the work. We can't just educate people to do it  
15 differently. So the way you do that -- and we've  
16 talked about a number of those today -- do we  
17 change PPAF form to an attestation form? Do we  
18 have a prior authorization, a prior authorization  
19 on refills? Do we engage the pharmacist more on  
20 the refill process, engage and ask questions  
21 differently than we do today. All of those kinds  
22 of things are things that can help accomplish the



1       tangible outcomes of 1 and 2.

2               Education, this really isn't doing it, at  
3       least not doing it terribly effectively. But I'm  
4       not sure that should be a primary goal anyway. So  
5       how do we ensure a safe and effective use? And I  
6       think we've got to maybe rethink just how we've  
7       approached the REMS, and maybe it's not this  
8       agreement, I acknowledge these factors, but we  
9       actually attest to these factors.

10              DR. BATEMAN: I thought what you did in  
11       reading the goals was quite useful, and maybe  
12       people can just comment on the first part of the  
13       question, whether those remain the right goals for  
14       this REMS program.

15              (Pause.)

16              DR. BATEMAN: Page 12 of the FDA  
17       presentation.

18              DR. MEISEL: Slide 12, Dr. LaCivita's.

19              DR. BATEMAN: This is it. So maybe people  
20       can just read these and comment specifically, are  
21       these the right goals or should this be amended in  
22       any fashion.

1 Dr. Nelson?

2 DR. NELSON: These goals do not talk about  
3 cancer versus non-cancer pain, but that's in the  
4 PPAF. So I assume it should be here as well.

5 DR. BATEMAN: I don't think it's in the  
6 PPAF.

7 DR. NELSON: Yes, it is. It's the first  
8 bullet in the PPAF. It says, "I understand that  
9 the only indication for this medication is cancer  
10 pain." And I think that we might want to focus the  
11 goals and objectives on making until we have data  
12 to support the fact that this drug is safe and  
13 effective in people with other sorts of pain, my  
14 sense is this is a drug that's used for people with  
15 end-of-life cancer pain, and maybe we should focus  
16 it on that population, and not just make it a  
17 suggestion but make it a rule.

18 DR. BATEMAN: Okay. Fair enough. There's  
19 not a strict requirement. They certify that the  
20 patients have cancer pain, but -- right.

21 Dr. Sandbrink?

22 DR. SANDBRINK: Friedhelm Sandbrink,

1 Washington, DC. I want to actually emphasize that.  
2 There are the really hard-wired requirements, not  
3 in anybody who is not opioid tolerant; not in any  
4 child. And I think if you take that training,  
5 certainly, I think you understand that. In regard  
6 to the off-label use of non-cancer patients, it is  
7 vague. It says that it's indicated for cancer  
8 patients, but it doesn't say anywhere that you  
9 couldn't write it for non-cancer patients; whereas  
10 it is very clear that you cannot write it in a  
11 child.

12 So you do understand. There are these  
13 different kinds of information to providers. It  
14 clearly is a different form of messaging, and I am  
15 not sure that there's agreement that it shouldn't  
16 be allowed in patients who don't have cancer if  
17 they have severe pain and they require a medication  
18 like this. And I think this is why it is so vague.

19 We often hear -- and this is another  
20 example -- prescribing in patients where it's not  
21 appropriate, and then it says, "e.g., patients not  
22 opioid tolerant." And again, there are really a

1       few very hard-wired requirements in this only, and  
2       I think those are being transmitted. But a lot of  
3       it is left open, and I don't think we have a  
4       consensus here that they should be mandated.

5               DR. BATEMAN: Other comments? Dr. Litman?

6               DR. LITMAN: I agree, with all due respect,  
7       to my colleagues. I don't agree that it should be  
8       limited to patients with cancer. Then the other  
9       thing I heard today was end of life. What does end  
10      of life mean, and what barriers or what border does  
11      that begin? To me, pain is pain, and obviously  
12      everybody's perception of pain is different no  
13      matter what they have. But if you're suffering,  
14      and this drug will help you, I think you should be  
15      allowed to have it.

16              So I am not in favor of the cancer only. I  
17      understand that it hasn't been proven safe and  
18      efficacious and other things, but to me that's  
19      beside the point. The tolerance is the safety  
20      thing, as we've been talking about.

21              DR. BATEMAN: Dr. Warner?

22              DR. WARNER: Thanks. I just wanted to go

1 back to the previous discussion a little bit about  
2 the timing and the length of the training. A  
3 couple of the panelists made some points about the  
4 concept that the training for this particular drug  
5 was less than other types of drugs, and it seems  
6 like it should be relative to the -- I understand  
7 the concept that the training may not be helpful or  
8 the education. There was a lot of discussion about  
9 how much education there should be. But the  
10 education should be in rank with the type of drug  
11 that's used.

12 So I don't know whether there's any way to  
13 look at the different new opioids that now have  
14 REMS that require some kind of training and how to  
15 rank order that training with this drug.

16 DR. BATEMAN: Other comments? Dr. Katzman?

17 DR. KATZMAN: Yes, I would agree with Dr.  
18 Warner on that. And I might be Pollyannish and  
19 slightly kind of respectfully disagree with some  
20 other folks, that I do agree that -- I think  
21 education very much can be helpful or at least a  
22 relook at the education that is currently being

1       used for the prescribers and the patients, and that  
2       I think there could be a few little tweaks on the  
3       education, even if it's not longer in terms of  
4       making it a little more efficacious to have a  
5       little more emphasis on whether it's cancer pain or  
6       severe pain, let's say, for not only cancer but  
7       complex regional pain syndrome or severe pains, and  
8       just emphasizing the risks of this.

9               I also am wondering, we haven't talked about  
10       it today, but how many of these patients have  
11       opiate-use disorder? We did not mention this at  
12       all this afternoon, and I would bet a million bucks  
13       that a significant percentage of these patients  
14       have opiate-use disorder and are not being treated.  
15       That's just one thing I want to put out there.

16               The other thing we didn't talk about is  
17       education to these prescribers about screening  
18       tools for addiction, and then again, reiterating  
19       the fact that these patients should probably be  
20       co-prescribed naloxone. Thank you.

21               DR. BATEMAN: Dr. Brand?

22               DR. BRAND: Paul Brand, Florence. One last

1       comment here. And the one thing we haven't talked  
2       about is we do have a tool out there that would  
3       solve a few of these problems already in place in  
4       the retail pharmacy setting, and that's what  
5       Dr. Warholak mentioned earlier, and that's  
6       prescription benefit managers, or PBMs as we call  
7       it. We haven't really engaged them in the fact  
8       that they could put a hard stop on each  
9       prescription and force you to call in and say, yes,  
10      this patient has been shown to be opioid tolerant.  
11      Right there, that solves that problem. Yes, the  
12      prescriber wrote on the prescription, "This  
13      diagnosis, that solves that problem."

14               Those are already in place for many, many  
15      other drugs, and it'd be super easy to do that.

16               DR. BATEMAN: Other comments?

17               (No response.)

18               DR. BATEMAN: To summarize our discussion on  
19      point 4, I think most on the committee felt that  
20      the goals and objectives of the TIRF REMS are still  
21      appropriate. There is some controversy about  
22      whether the REMS should be strengthened with

1       respect to the issue of use in non-cancer pain and  
2       whether there should be a certification on the PPAF  
3       that the patients have not only opioid tolerance  
4       but also cancer breakthrough pain, which is the  
5       indication for the medication.

6               In terms of part B, the way that they REMS  
7       is designed, there were a number of suggestions for  
8       approaches to potentially strengthening the REMS  
9       program, including improving the approach to  
10       education and various systems-based approaches to  
11       ensuring that the knowledge conveyed in the REMS  
12       are actuated in practice.

13              Anything else to add to my summary there?

14              (No response.)

15              DR. BATEMAN: Okay.

16              Before we adjourn, are there any comments  
17       from the FDA?

18              DR. STAFFA: Judy Staffa here. I just  
19       wanted to thank you very much. We know this has  
20       been a long day. We know we presented a lot of  
21       information as to did the TRIG, and we know we  
22       asked a lot of questions. And we appreciate your



1 persistence and your advice and recommendations.  
2 It's very helpful, and we'll include that in all of  
3 our deliberations. So thank you.

4 **Adjournment**

5 DR. BATEMAN: Thank you.

6 Panel members, please take all personal  
7 belongings with you as the room is cleaned at the  
8 end of the meeting day. All materials left on the  
9 table will be disposed of. Please also remember to  
10 drop off your name badge at the registration table  
11 on your way out so they may be recycled. We'll now  
12 adjourn the meeting. Thank you.

13 (Whereupon, at 4:51 p.m., the meeting was  
14 adjourned.)  
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